



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

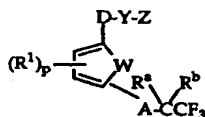
(51) International Patent Classification ⁶ : A61K		A2	(11) International Publication Number: WO 99/15129
			(43) International Publication Date: 1 April 1999 (01.04.99)
(21) International Application Number: PCT/US98/19426			(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
(22) International Filing Date: 17 September 1998 (17.09.98)			
(30) Priority Data: 60/059,597 23 September 1997 (23.09.97) US 60/063,518 27 October 1997 (27.10.97) US			
(71) Applicant: BRISTOL-MYERS SQUIBB COMPANY [US/US]; 5 Research Parkway, Wallingford, CT 06492 (US).			
(72) Inventors: BANVILLE, Jacques; 1209 Girard, St-Hubert, Quebec J4T 1H3 (CA). GAI, Yonghua; 325 François Leber, La Prairie, Quebec J5R 5M1 (CA). JOHNSON, Graham; 57 Bridle Path Lane, Madison, CT 06443 (US). ZUSI, Fred, Christopher; 10 Nolan Road, Hamden, CT 06514 (US). BURKE, James, R.; 32 Windridge Court, Williamsville, NY 14221 (US).			
(74) Agent: MORSE, David, M.; Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, CT 06492 (US).			

Published

Without international search report and to be republished upon receipt of that report.

31355 U.S. PTO
10/758240

011604

(54) Title: SELECTIVE cPLA₂ INHIBITORS

(i)

(57) Abstract

Selective inhibitors of the cPLA₂ enzymes are provided which are of use in controlling a wide variety of inflammatory diseases. The inhibitors of the present invention have general formula (i), where (R¹), p, D, Y, Z, R^a, R^b and A are as defined in the specification.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

SELECTIVE cPLA₂ INHIBITORS

BACKGROUND OF THE INVENTION

5 Inflammatory diseases of the skin, such as psoriasis and atopic dermatitis, afflict greater than 5% of the population. Currently, the treatment of these disorders typically involves the use of topical steroids. However, these agents also have undesirable side effects such as skin atrophy which limit the duration of therapy. In addition, topical
10 application of a drug is difficult for many patients where the affected area may be very large.

 Phospholipase A₂ (PLA₂) is the common name for phosphatide 2-acylhydrolase which catalyzes the hydrolysis of the sn-2-acyl ester bond of
15 phosphoglycerides and results in production of lysophospholipids and free fatty acids. When the fatty acid is arachidonic acid, further action by cyclooxygenase and 5-lipoxygenase enzymes results in eicosanoid production, which is implicated in inflammation, and leukotrienes which are linked to asthma. Lysophospholipid metabolism results in
20 production of platelet activating factor and both lysophospholipids and platelet activating factor also play a role in inflammation.

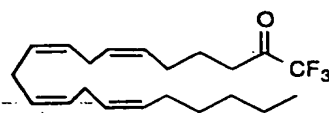
 PLA₂ enzymes exist as secreted forms (MW ~ 12,000-15,000) and cytosolic forms (MW ~ 85,000). The cytosolic or cPLA₂ enzymes appear
25 play a key role in the pathway leading to the formation of platelet activating factor and the eicosanoids.

Inappropriate activation of the cytosolic PLA₂ enzymes, therefore, can result in a variety of chronic and acute conditions including asthma, cerebral ischemia (Clemens et al, Stroke, 1996, 27, 527-535), Alzheimer's Disease (Stephenson et al, Neurobiology of Stroke, 1996, 3, 51-63 and see
5 also U.S. Patent 5,478,857), rheumatoid arthritis, neutrophil and platelet activation (Huang et al, Mediators of Inflammation, 1994, 3, 307-308), chronic skin inflammation and damage to the skin resulting from exposure to ultraviolet light (Gresham et al., American Journal of Physiology, 1996, 270; Cell Physiology 39:C1037-C1050) and macrophage
10 activation (Balsinde et al, Journal of Biological Chemistry, 1996, 271, 6758-6765).

Selective inhibitors of the cPLA₂ enzymes may, therefore, be of use in controlling a wide variety of inflammatory diseases. The literature
15 describes a significant number of compounds said to be phospholipase A₂ inhibitors, but few selective inhibitors for the cPLA₂ enzymes are available. The present inventors had as their goal the synthesis of novel compounds which would be selective and potent inhibitors of the cPLA₂ enzymes. As used herein, the term "selective inhibitors of the cPLA₂
20 enzymes" means that the inhibitors inhibit the cPLA₂ enzymes with a potency 20-fold or greater than they inhibit the lower molecular weight synovial PLA₂ enzymes.

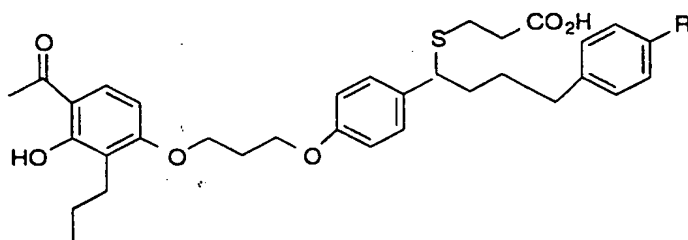
Biochemistry 32: 5935-5940, 1993, discloses a trifluoromethyl ketone
25 analog of arachidonic acid having the formula

3



as a selective inhibitor of cPLA₂.

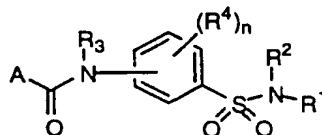
- 5 Bioorganic Med. Chem. Lett. 5: 519-522, 1995, discloses selective cPLA₂ inhibitors of the formula



- 10 where R is either H or OH.

Japanese published patent application JP09268153A (Derwent No. 97-554679/51) discloses cPLA₂ inhibitors of the formula RCOCF₃ where RCO is an acyl residue of an n-3 series highly unsaturated fatty acid. The
15 compounds are said to be useful as antiinflammatory or antiallergic drugs.

Published PCT Application WO 98/25893 discloses arylsulfonamide compounds of the general formula



20

wherein

4

A represents a C₄-C₁₀ alkyl group, an aryl group, an arylalkyl group, radicals selected from the group consisting of —CH=CH—B, —O—B, —S—B, and —NH—B, or radicals of formula —CH₂—X,

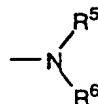
5

wherein

B represents a non-aromatic C₃-C₈ carbocycle, a C₃-C₈ alkyl group, a heterocycle or an arylalkyl group, each of which is optionally substituted with one or more members independently selected from the group consisting of a halogen atom, a C₁-C₄ alkyl group, a C₁-C₄ alkoxy group, cyano, nitro, a heterocycle, an aryl group and an aryloxy group, and

X is a member selected from the group consisting of a halogen atom, —S—aryl, —S—heterocycle, and —PO₃R₂ wherein each R is independently selected from the group consisting of a hydrogen atom and C₁-C₃ alkyl;

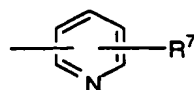
R¹ and R² each independently represent a hydrogen atom, a lower alkyl group, or a group represented by the formula: —(CH₂)_q—A' wherein q is an integer of 2 to 4, and A' is a member selected from the group consisting of a hydroxyl group, a group represented by the formula:



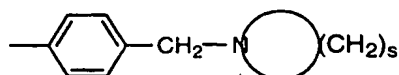
25

wherein R⁵ and R⁶ each independently represent a hydrogen atom, a lower alkyl group, or a group represented by the formula:

5



wherein R^7 represents a hydrogen atom, a lower alkyl group, or a group
 5 represented by the formula:

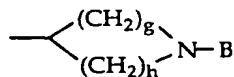


wherein s is an integer of 2 to 5; or

10

R^1 and R^2 each independently represent an unsubstituted cycloalkyl group, or a cycloalkyl substituted with a lower alkyl or halogen or condensed with an aromatic ring, a bicycloalkyl, or tricycloalkyl, said bicycloalkyl or tricycloalkyl being an aliphatic saturated hydrocarbon
 15 group made of two or three rings, respectively, with at least two carbon atoms being common to each ring, or an azabicycloalkyl group which is a bicycloalkyl group as described above in which one carbon atom is replaced by a nitrogen atom or a group represented by the formula:

20



wherein g and h are each an integer of 1 to 4, and B' stands for a lower alkyl group, an arylalkyl group, an arylalkyl group substituted by lower alkyl; halogen or a lower alkoxy group, or a pyridylalkyl group, or a
 25 pyridylalkyl group substituted with a lower alkyl group, a halogen or a lower alkoxy group; or

b

R¹ and R² may be combined together to form a 6- or 7-membered ring which may contain a nitrogen or oxygen atom in addition to the nitrogen atom to which R¹ and R² are bonded, and said 6- or 7-membered ring may
5 be substituted with a lower alkyl, arylalkyl, cycloalkylalkyl or heteroarylalkyl group;

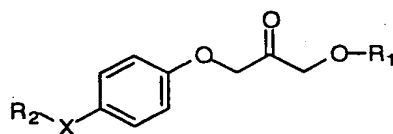
R³ represents a hydrogen atom, a lower alkyl group, or a C₃-C₈ cycloalkyl group;

10

R⁴ represents a hydrogen atom, a lower alkyl group, a lower alkoxy group or a halogen atom;

n is an integer of 1 to 4, provided that when n is 2, the two R⁴ groups may
15 form a cyclohexenyl or phenyl ring together with two adjacent carbon atoms constituting the benzene ring; and any pharmacologically acceptable salts thereof as inhibitors of phospholipase A₂ activity, particularly cPLA₂.

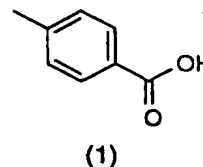
20 Drugs 1998, Vol. 1, No. 1, pp. 49-50 discloses cPLA₂ inhibitors of the type



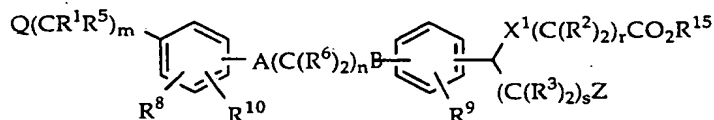
25

7

R_1	R_2	X
CH_3	$CH_3(CH_2)_9$	O
(1)	$CH_3(CH_2)_9$	O
(1)	$Ph(CH_2)_5$	S
(1)	$CH_3(CH_2)_9$	SO_2



U.S. Patent 5,453,443 discloses a series of biaryl ketones which are reported to inhibit PLA_2 enzymes, but it is not indicated whether these compounds are selective for the cytosolic enzymes or even whether they inhibit the cytosolic enzymes. These compounds have the generic formula



10

wherein:

R^1 is selected from

- 15 (a) hydrogen,
- (b) $-C_{1-6}$ alkyl, and
- (c) $-C_{1-6}$ alkyl-phenyl;

20

or wherein R^1 and R^5 are joined such that together with the carbon atoms to which they are attached there is formed a saturated or unsaturated carbon ring of 3, 4, 5, 6, 7 or 8 atoms;

R^2 and R^3 are each independently selected from

(a) hydrogen,

(b) — C₁₋₆alkyl, and

5 (c) — C₁₋₆alkyl-phenyl,

or wherein two R² or two R³ are joined such that together with the carbon atoms to which they are attached there is formed a saturated or unsaturated carbon ring of 3, 4, 5, 6, 7 or 8 atoms;

10

R⁵ is as defined above or is selected from

(a) hydrogen

15 (b) — C₁₋₆alkyl,

(c) — C₁₋₆alkyl-phenylC₁₋₆alkyl,

(d) — OH,

20

(e) — O — C₁₋₆alkyl, or

(f) — C₁₋₆alkyl-phenylC₁₋₆alkyl;

25 R⁶ is selected from

(a) hydrogen

9

(b) $-C_{1-6}\text{alkyl}$,(c) $-C_{1-6}\text{alkyl-phenyl}$, wherein the phenyl is optionally substituted with $C_{1-2}\text{alkyl}$;

5

(d) $-\text{OH}$,(e) $-\text{O}-C_{1-6}\text{alkyl}$, or

10

(f) $-\text{O}-C_{1-6}\text{alkyl-phenyl}$, wherein the phenyl is optionally substituted with $C_{1-2}\text{alkyl}$;

or wherein two R^6 are joined to form $\text{O}=\text{O}$ or are joined together such that together with the carbon atom to which they are attached there is
15 formed a saturated or unsaturated carbon ring of 3, 4, 5, 6, 7 or 8 atoms;

R^8 , R^9 and R^{14} are each independently selected from

(a) H,

20

(b) $-C_{1-6}\text{alkyl}$,

(c) halo

25

(d) $-\text{CN}$ (e) $-\text{OH}$

10

- (f) $-\text{OC}_{1-6}\text{alkyl}$,
- (g) $-\text{OC}_{1-6}\text{alkyl-phenyl}$,
- 5 (h) $-\text{SR}^{11}$
- (i) S(O)R^{11} , or
- (j) $\text{S(O)}_2\text{R}^{11}$;

10

R^{10} , R^{15} , R^{16} and R^{17} are each independently selected from

- (a) hydrogen,
- 15 (b) $-\text{C}_{1-6}\text{ alkyl}$, and
- (c) $-\text{C}_{1-6}\text{ alkyl-phenyl}$;

R^{11} is selected from

20

- (a) $-\text{C}_{1-6}\text{ alkyl}$,
- (b) $-\text{C}_{2-6}\text{ alkenyl}$,
- 25 (c) $-\text{CF}_3$,
- (d) $-\text{phenyl(R}^{12})_2$, or

11

(e) $-\text{C}_{2-6}$ alkenyl-phenyl(R^{12})₂,

R^{12} is

5 (a) hydrogen,

(b) $-\text{C}_{1-6}$ alkyl,

(c) Cl, F, I or Br;

10

R^{13} is perfluoro C_{1-6} alkyl;

A and B are each independently

15 (a) covalent bond,

(b) O,

(c) S,

20

(d) S(O), or

(e) S(O)_2 ;

25 Q is selected from

(a) $-\text{CH(OH)R}^{13}$,

12

- (b) $-\text{COR}^{13}$,
- (c) $-\text{COR}^{16}$, or
- 5 (d) $-\text{C}_{1-4}\text{alkylCOCOOR}^{17}$;

X^1 is selected from

- (a) $-\text{O}-$,
- 10 (b) $-\text{S}-$,
- (c) $-\text{S(O)}-$,
- 15 (d) $-\text{S(O)}_2-$;

Z is

- (a) H , or
- 20 (b) $-\text{phenyl}-(\text{R}^{14})_3$,

m is 0, 1, 2, 3 or 4;

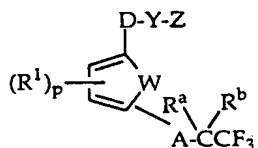
25 n is 2, 3, 4, 5, 6 or 7; and

r and s are each independently 0, 1, 2, 3, 4, 5, 6, 7 or 8.

B

SUMMARY OF THE INVENTION

The present invention is directed to selective cytosolic PLA₂ inhibitor compounds of the formula



5

I

wherein W is CH=CH, CH=N, O or S;

- 10 R¹ is (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)alkoxy, (C₁-C₆)alkylthio, halo, hydroxy, cyano, $-\overset{\text{O}}{\underset{\text{||}}{\text{C}}}-\overset{\text{R}^2}{\underset{\text{|}}{\text{N}}}-\text{R}^3$ in which R² and R³ are each independently hydrogen or (C₁-C₆)alkyl, -COO-(C₁-C₆)alkyl, CF₃, (C₁-C₆)alkylphenyl, phenyl or phenyl substituted by one or more, preferably 1-3, of (C₁-C₆)alkyl, -COO-(C₁-C₆)alkyl, $-\overset{\text{O}}{\underset{\text{||}}{\text{C}}}-\overset{\text{R}^2}{\underset{\text{|}}{\text{N}}}-\text{R}^3$ in which R² and R³ are as defined above, halo, hydroxy, -O-(C₁-C₆)alkyl, -S-(C₁-C₆)alkyl or (C₂-C₆)alkenyl;

15

p is 0, 1 or 2;

- 20 A is V-(R^c)_n -;

R^c is a straight or branched chain alkyl group;


n is 0 or an integer of from 1 to 6;

25

14

R^a and R^b when taken together form an oxo ($=O$) group, or R^a and R^b are each independently hydrogen or OH;

V is O, -S-, -SO-, -SO₂-, -CONH or NHCO when n is an integer of from 1 to 5 6 or V is (C₂-C₆) alkenyl or a bond when n is 0 or an integer of from 1 to 6;

D is -(CH₂)_m or a bond linking the  ring to Y;

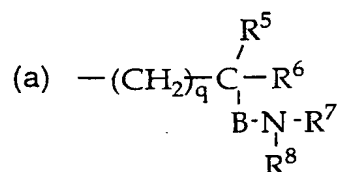
m is an integer of from 1 to 6;

10

Y is -O-, -S-, -SO-, -SO₂-, $\overset{R^4}{\underset{|}{N}}$ - or a bond;

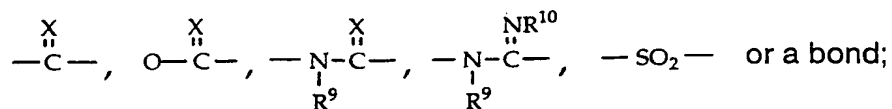
R^4 is as defined below for R^7 ;

15 Z is:



in which B is:

20



X is S or O;

25 q is an integer from 1 to 6;

15

R⁹ is hydrogen or (C₁-C₆)alkyl;

R¹⁰ is hydrogen, CN, NO₂, OH, -O-(C₁-C₆)alkyl, (C₁-C₆) alkyl, phenyl or
5 (C₁-C₆)alkylphenyl;

R⁵ and R⁶ are each independently hydrogen or (C₁-C₁₈) alkyl;

R⁷ and R⁸ are each independently;

10

(a) hydrogen;

(b) (C₁-C₁₈)alkyl;

15 (c) (C₁-C₁₈)alkyl substituted by one or more of

(1) phenyl;

20 (2) phenyl substituted by 1-5 fluoro, 1-3 (for each of the following
phenyl substituents) halo (other than fluoro), 1-3
(C₁-C₆)alkoxy, 1-3(C₁-C₆)alkyl, nitro, cyano, hydroxy,
trifluoromethyl, (C₁-C₆)alkylthio, amino, 1-3
(C₁-C₆) alkylamino, di(C₁-C₆)alkylamino, -CO₂H, -COO-
(C₁-C₆)alkyl, -SO₃H, -SO₂NHR¹⁵ in which R¹⁵ is hydrogen
25 or (C₁-C₆)alkyl, or $\begin{array}{c} \text{O} \\ \parallel \\ -\text{C}-\text{N}-\text{R}^3 \end{array} \begin{array}{c} \text{R}^2 \\ | \end{array}$ in which R² and R³ are as
defined above;

- (3) heterocyclic selected from oxadiazolyl, isoxazolyl, oxazolyl, furyl and thiazolyl;
- (4) heterocyclic substituted by one or more of, preferably 1-3, phenyl, phenyl substituted by 1-3 (for each of the following) halo, (C₁-C₆)alkoxy, (C₁-C₆)alkyl, nitro, cyano, hydroxy, trifluoromethyl, (C₁-C₆) alkylthio, amino, (C₁-C₆) alkylamino, di(C₁-C₆) alkylamino, CO₂H, -COO-(C₁-C₆) alkyl, -SO₃H, SO₂NHR¹⁵ in which R¹⁵ is hydrogen or (C₁-C₆) alkyl, or
- $$-\overset{\overset{\text{O}}{\parallel}}{\text{C}}-\overset{\overset{\text{R}^2}{\mid}}{\text{N}}-\text{R}^3$$
- in which R² and R³ are as defined above, (C₁-C₆) alkyl or (C₁-C₆) alkyl substituted by one or more, preferably 1-3, phenyl or heterocyclic groups, said phenyl or heterocyclic group being unsubstituted or substituted by 1-3 (for each of the following) halo, 1-3 (C₁-C₆) alkoxy, 1-3 (C₁-C₆) alkyl, nitro, cyano, hydroxy, trifluoromethyl, (C₁-C₆) alkylthio, amino, 1-3 (C₁-C₆) alkylamino, di(C₁-C₆) alkylamino, COOH, -COO-(C₁-C₆) alkyl, -SO₃H, -SO₂NHR¹⁵ in which R¹⁵ is hydrogen or (C₁-C₆) alkyl, or
- $$-\overset{\overset{\text{O}}{\parallel}}{\text{C}}-\overset{\overset{\text{R}^2}{\mid}}{\text{N}}-\text{R}^3$$
- in which R² and R³ are each independently hydrogen or (C₁-C₆) alkyl, the heterocyclic radical being selected from imidazolyl, oxadiazolyl, isoxazolyl, pyrrolyl, pyrazolyl, oxazolyl, furyl, thianyl or thiazolyl;
- (5) carboxy or -COO-(C₁-C₆) alkyl;

17

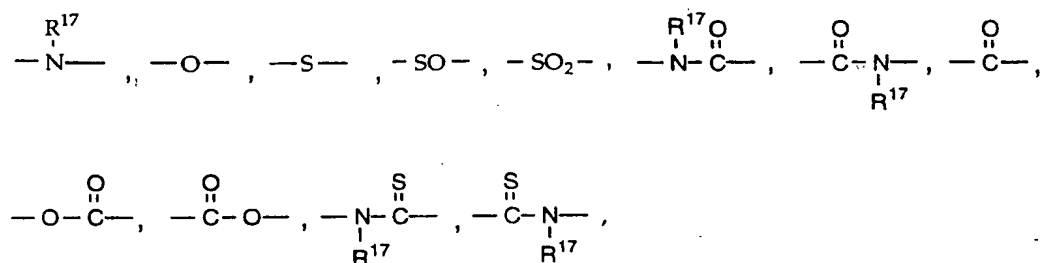
(6) hydroxy, halo, -O-(C₁-C₆) alkyl or -S-(C₁-C₆) alkyl, with the proviso that the OH, ethers or thioethers cannot be on the carbon bearing the heteroatoms;

5 (7) cyano;

(8) halo, trifluoromethyl or trifluoroacetyl;

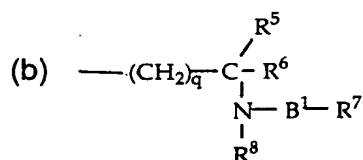
(9) CH₂ L-R¹⁶ in which L is

10

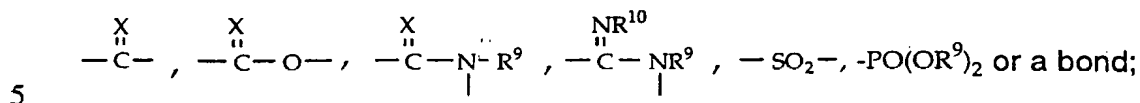


or -O-SiR¹⁶R¹⁸R¹⁹ or a bond in which R¹⁶ and R¹⁷ are each independently (C₁-C₁₈)alkyl or (C₂-C₁₈)alkenyl or (C₁-C₁₈)alkyl or
 15 (C₂-C₁₈)alkenyl substituted by one or more, preferably 1-3, phenyl or heterocyclic radicals, said phenyl or heterocyclic radicals being unsubstituted or substituted by 1-5 fluoro, 1-3 halo (other than fluoro), 1-3 (C₁-C₆)alkoxy, 1-3(C₁-C₆)alkyl, nitro, cyano, hydroxy, 1-3 trifluoromethyl, 1-3 (C₁-C₆)alkylthio, amino, 1-3(C₁-C₆)alkylamino,
 20 1-3 di(C₁-C₆)alkylamino, CO₂H, 1-3 -COO(C₁-C₆)alkyl, $-\overset{\text{O}}{\text{C}}-\overset{\text{R}^2}{\text{N}}-\text{R}^3$ or -SO₂NHR⁹ in which R⁹ is hydrogen or (C₁-C₆)alkyl and R² and R³ are as defined above;

18



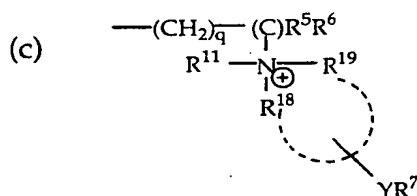
in which B¹ is



providing that when B¹ is $\text{---PO(OR}^9)_2\text{---}$, then R⁷ becomes R⁹, and when B¹ is $\text{---}\overset{\text{X}}{\underset{\text{||}}{\text{C}}}\text{---O---}$ or $\text{---SO}_2\text{---}$, then R⁷ cannot be hydrogen;

X, q, R⁵, R⁶, R⁷, R⁸, R⁹ and R¹⁰ are as defined in (a);

10



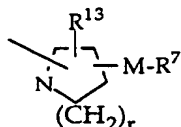
in which q, R⁵ and R⁶ are as defined above;

- 15 R¹⁸, R¹⁹ and R¹¹ are as defined above for R⁷ and R⁸ except that they may not be hydrogen, or R¹⁸ and R¹⁹ taken together with the nitrogen to which they are attached represent a 4, 5- or 6-membered heterocyclic ring and Y, R⁷ and R¹¹ are as defined above, or R¹⁸, R¹⁹ and R¹¹ taken together with the nitrogen to which they are attached represent
- 20 pyridinium, said pyridinium group being unsubstituted or substituted by (C1-C12)alkyl, (C1-C12)alkoxy, amino, (C1-C12)alkylamino, di

19

(C₁-C₁₂)alkylamino, $-\overset{\text{O}}{\parallel}{\text{C}}-\text{O}-$ (C₁-C₆)alkyl, -S-(C₁-C₁₂)alkyl, $-\overset{\text{O}}{\parallel}{\text{C}}-\overset{\text{R}^2}{\text{N}}-\text{R}^3$ in which R² and R³ are as defined above, phenyl or phenyl (C₁-C₁₀)alkyl;

5 d)



- in which R¹³ is (C₁-C₁₈)alkyl or (C₁-C₁₈)alkyl substituted by carboxy, $-\overset{\text{O}}{\parallel}{\text{C}}-\text{O}-$ (C₁-C₁₂) alkyl, $-\overset{\text{O}}{\parallel}{\text{C}}-\overset{\text{R}^2}{\text{N}}-\text{R}^3$ in which R² and R³ are as defined above, hydroxy, -O-(C₁-C₆) alkyl, -O-(C₁-C₆) alkyl or -S-(C₁-C₆) alkyl substituted by 1 or 2 phenyl or substituted phenyl groups, the substituents for the substituted phenyl groups being 1-5 fluoro or 1-3 (for each of the following phenyl substituents) halo (other than fluoro), (C₁-C₆) alkoxy, (C₁-C₆) alkyl, nitro, cyano, hydroxy, trifluoromethyl, (C₁-C₆) alkylthio, amino, (C₁-C₆) alkylamino, di(C₁-C₆) alkylamino, CO₂H, COO-(C₁-C₆) alkyl, SO₃H, SO₂NHR¹⁵ in which R¹⁵ is hydrogen or (C₁-C₆) alkyl or $-\overset{\text{O}}{\parallel}{\text{C}}-\overset{\text{R}^2}{\text{N}}-\text{R}^3$ in which R² and R³ are as defined above;

r is 0 or an integer of from 1 to 3;

20 R⁷ is as defined above;

M is -(CH₂)_mT where T is $-\overset{\text{O}}{\parallel}{\text{C}}-$, $-\overset{\text{O}}{\parallel}{\text{C}}-\text{O}$, $-\overset{\text{O}}{\parallel}{\text{C}}-\overset{\text{R}^2}{\text{N}}-$, in which R² is as defined above, -SO₂- or a bond when MR⁷ is on nitrogen and providing that when T is $-\overset{\text{O}}{\parallel}{\text{C}}-$ or -SO- or -SO₂-, then R⁷ cannot be hydrogen, and T

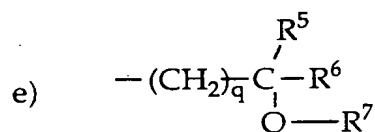
20

is $-\overset{\text{O}}{\parallel}{\text{C}}-$, $-\overset{\text{O}}{\parallel}{\text{C}}-\text{O}-$, $-\text{O}-$, $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$, $-\overset{\text{R}^{14}}{\text{N}}-$ or a bond when MR^7 is on a carbon atom of the heterocyclic ring;

R^{14} is hydrogen or (C_1-C_6) alkyl;

5

m is 0 or an integer of 1-6;



10 wherein Q is $-\text{O}-$, $-\text{S}-$, $-\text{SO}-$ or $-\text{SO}_2-$, and q , R^5 , R^6 and R^7 are as defined above, providing that when Q is $-\text{SO}-$ or $-\text{SO}_2-$, R^7 cannot be hydrogen;

f) R^7 wherein R^7 is defined above, providing that when Y is $-\text{SO}-$ or $-\text{SO}_2-$, R^7 cannot be hydrogen; and

15

R^{18} and R^{19} are phenyl or phenyl substituted by 1-3 halo, (C_1-C_6) alkoxy, (C_1-C_6) alkyl, nitro, cyano, hydroxy, trifluoromethyl, (C_1-C_6) alkylthio, amino, (C_1-C_6) alkylamino, $\text{di}(\text{C}_1-\text{C}_6)$ alkylamino, CO_2H , $-\text{COO}-(\text{C}_1-\text{C}_6)$ alkyl, $-\text{SO}_3\text{H}$, $\text{SO}_2\text{NHR}^{15}$ in which R^{15} is
 20 hydrogen or (C_1-C_6) alkyl, or $-\overset{\text{O}}{\parallel}{\text{C}}-\overset{\text{R}^2}{\underset{|}{\text{N}}}-\text{R}^3$ in which R^2 and R^3 are as defined above; or pharmaceutically acceptable salts, solvates or prodrugs thereof.

Also provided by this invention are methods for inhibiting
 25 cytosolic PLA_2 in a mammal in need thereof which comprises administering to said mammal a therapeutically effective amount of a

21

compound of formula I and methods for using the compounds of formula I to treat various diseases characterized by inappropriate activation of the cytosolic PLA₂ enzymes such as asthma, allergic rhinitis, cerebral ischemia, Alzheimer's Disease, rheumatoid arthritis, acute
5 pancreatitis, inflammatory bowel disease, psoriasis, gout, neutrophil and platelet activation, chronic skin inflammation, shock, trauma-induced inflammation such as spinal cord injury, damage to the skin resulting from UV light or burns and macrophage activation. In further aspects, the present invention provides pharmaceutical compositions comprising
10 a therapeutically effective amount of a compound of formula I and a pharmaceutically acceptable carrier and processes for preparing the compounds of formula I.

DETAILED DESCRIPTION

15

The object of this invention was to discover a selective cPLA₂ inhibitor which is active, both topically and orally, in treating inflammatory disease of the skin and other tissues as well as other chronic and acute conditions which have been linked to inappropriate activation of the
20 cPLA₂ enzymes. Preferably such compound would also be devoid of undesirable lipid-perturbing activities associated with skin irritation.

The above-mentioned objectives have been met by the compounds of formula I described above.

25

In the present application the numbers in the subscript after the symbol "C" define the number of carbon atoms a particular group can contain. For example, C₁₋₁₈alkyl refers to straight and branched chain alkyl

groups with 1 to 18 carbon atoms. Similarly, C₂-C₁₈ alkenyl refers to a straight or branched unsaturated hydrocarbon group containing from 2 to 18 carbon atoms and at least one carbon-carbon double bond. Likewise, C₂-C₁₈ alkynyl refers to a straight or branched unsaturated hydrocarbon group containing from 2 to 18 carbon atoms and at least one carbon-carbon triple bond.

The term "halogen" or "halo" as used herein refers to fluorine, chlorine, bromine or iodine.

10

Aryl as used herein refers to a C₆ monocyclic aromatic ring system or a C₉ or C₁₀ bicyclic carbocyclic ring system having one or two aromatic rings such as phenyl or naphthyl. Unless otherwise indicated, "substituted aryl" refers to aryl groups substituted with one or more (preferably from 1 to 3) substituents independently selected from (C₁-C₆)alkyl, haloalkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkoxy-carbonyl, (C₁-C₆)alkanoyl, hydroxy, halo, mercapto, nitro, amino, cyano, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, carboxy, aryl, aryl (C₁-C₆)alkyl, aryl (C₁-C₆)alkoxy, heterocyclic, heterocyclic (C₁-C₆)alkyl and the like.

20

The term "heterocyclic" as used herein refers to a 4-, 5- or 6-membered ring containing one, two or three heteroatoms selected from N, O and S. The 5-membered ring has 0-2 double bonds and the 6-membered ring has 0-3 double bonds. The nitrogen heteroatoms can be optionally quaternized or N-oxidized. The sulfur heteroatoms can be optionally S-oxidized. The term "heterocyclic" also includes bicyclic groups in which any of the above heterocyclic rings is fused to a benzene ring or a cyclohexane ring or another heterocyclic ring. Heterocyclics

include: pyrrolyl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, imidazolyl, imidazolidinyl, pyridyl, piperidyl, pyrazinyl, piperazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolinyl, oxazolidinyl, isoxazolyl, isoxazolinyl, isoxazolidinyl, morpholinyl, thiazolyl, 5 thiazolidinyl, isothiazolyl, isothiazolidinyl, indolyl, quinolinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, benzofuranyl, furyl, dihydrofuranyl, tetrahydrofuranyl, pyranyl, dihydropyranyl, dioxolanyl, thienyl, benzothienyl and diaxanyl.

10 Some of the compounds described herein contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention is meant to include such possible diastereomers as well as their racemic and resolved, enantiomerically pure forms, and pharmaceutically acceptable salts thereof.

15 As mentioned above the invention also includes pharmaceutically acceptable salts of the compounds of formula I. A compound of the invention can possess a sufficiently acidic, a sufficiently basic, or both functional groups. Accordingly, a compound may react with any of a 20 number of inorganic bases, and organic and inorganic acids, to form a pharmaceutically acceptable salt.

 The term "pharmaceutically acceptable salt" as used herein refers to salts of the compounds of formula I which are substantially non-toxic to 25 living organisms. Typical pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the present invention with a pharmaceutically acceptable mineral or organic acid or an inorganic base. Such salts are known as acid addition and base addition salts.

Acids commonly employed to form acid addition salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as p-toluenesulfonic, methanesulfonic acid, oxalic acid, p-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like. Examples of such pharmaceutically acceptable salts are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogen phosphate, dihydrogen phosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caproate, heptanoate, propionate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xylene-sulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, γ -hydroxybutyrate, glycolate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and the like. Preferred pharmaceutically acceptable acid addition salts are those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and those formed with organic acids such as maleic acid and methanesulfonic acid.

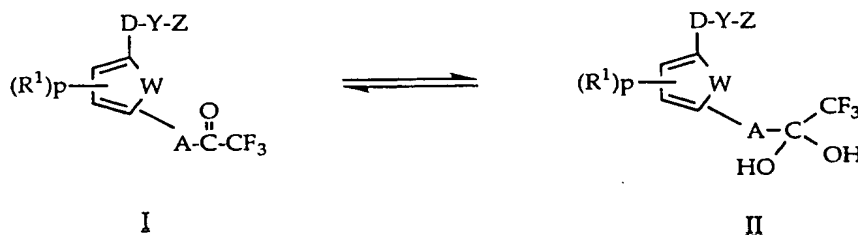
Base addition salts include those derived from inorganic bases, such as ammonium or alkali or alkaline earth metal hydroxides, carbonates, bicarbonates, and the like. Such bases useful in preparing the salts of this invention thus include sodium hydroxide, potassium hydroxide, ammonium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like. Suitable organic bases include trialkylamines such as

25

triethylamine, procaine, dibenzylamine, N-benzyl- β -phenethylamine, 1-
 ephenamine, N,N'-dibenzylethylene-diamine, dehydroabietylamine, N-
 ethylpiperidine, benzylamine, dicyclohexylamine, or the like
 pharmaceutically acceptable amines. The potassium and sodium salt
 5 forms are particularly preferred.

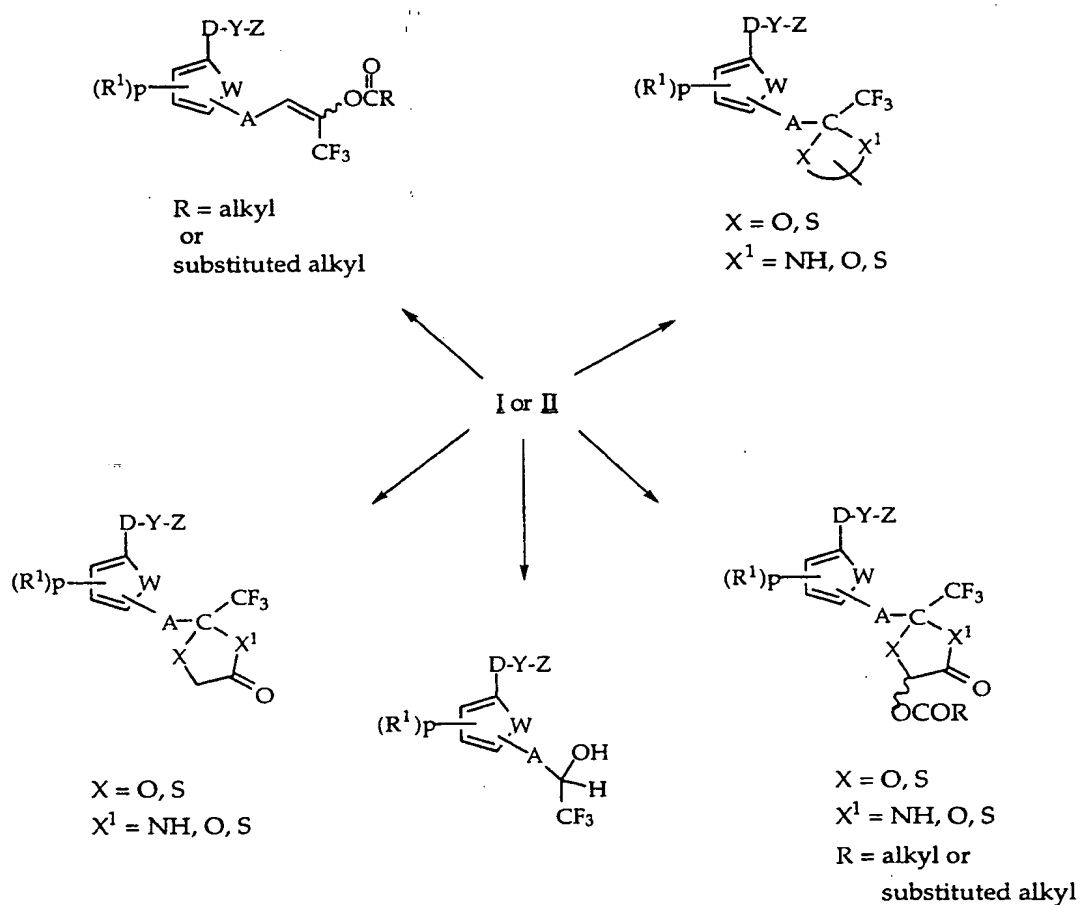
It should be recognized that the particular counterion forming a
 part of any salt of this invention is usually not of a critical nature, so long
 as the salt as a whole is pharmacologically acceptable and as long as the
 10 counterion does not contribute undesired qualities to the salt as a whole.

The present invention also includes solvated forms of the
 compounds of formula I, particularly hydrates, in which the
 trifluoromethyl ketone group exists as a mixture of ketonic I and hydrated
 15 forms II and are each independently interconvertible and
 pharmacologically active.



20 The present invention also includes prodrug forms of the
 compounds of formula I or II above such as trifluoromethylketone enol
 ester derivatives, enol phosphate derivatives, cyclic or acyclic
 unsubstituted or substituted O,O-ketals, O,S-ketals, O,N-ketals or S,N-
 ketals such as cyclic cysteamyl derivatives, cyclic glycolates, thioglycolates,
 25 glyoxylates or oxalates, and the like. It also includes

trifluoromethylalcohols obtained by chemical reduction of trifluoromethylketones. Such forms are physiologically hydrolyzable groups which are converted *in vivo* to a pharmacologically active compound of formula I or II, or a crystalline form of such compounds, see scheme below.



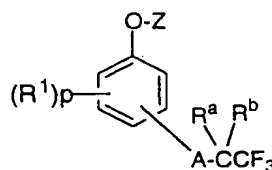
10

Preferred compounds of formula I are those where the -A-CCF_3 substituent is linked to the phenyl ring at the para or meta position, most preferably at the para position.

Preferred embodiments of the compounds of general formula I include

- (a) compounds of formula I wherein W is CH=CH, D is a bond linking Y to the ring and Y is -O-;
- (b) compounds of (a) immediately above wherein R¹ is benzyl, A is V-(CH₂)_n-, V is (C₂-C₆) alkenyl or a bond, p is 0, 1 or 2, and n is 0 or an integer of from 1 to 6; and
- (c) compounds of (b) immediately above wherein A is -(CH₂)_n-, n is 0 or an integer of from 1 to 6, and the group -(CH₂)_nCOCF₃ is in the meta or para position of the phenyl ring.

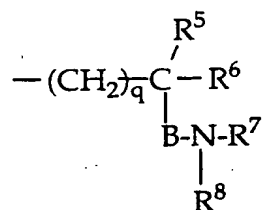
Another preferred embodiment comprises a compound of the formula



- wherein R¹ is benzyl; p is 0, 1 or 2; A is V-(CH₂)_n-, V is (C₂-C₆) alkenyl or a bond; n is 0 or an integer of from 1 to 6; R^a and R^b are as defined above and Z is

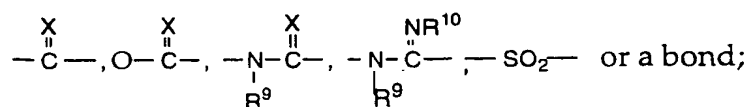
28

(a)



in which B is

5



X is S or O;

10 q is an integer of from 1 to 6;

R⁹ is hydrogen or (C₁-C₆) alkyl;

15 R¹⁰ is hydrogen, CN, NO₂, OH, -O-(C₁-C₆) alkyl, (C₁-C₆) alkyl, phenyl or (C₁-C₆) alkylphenyl;

R⁵ and R⁶ are each independently hydrogen or (C₁-C₆) alkyl; and R⁷ and R⁸ are each independently

- a) hydrogen;
- 20 b) (C₁-C₁₈) alkyl;
- c) (C₁-C₁₈) alkyl substituted by one or more of, preferably 1-3,
 - (1) phenyl;
 - (2) phenyl substituted by 1-5 fluoro, 1-3 halo (other than fluoro), 1-3 (C₁-C₆) alkoxy, 1-3 (C₁-C₆) alkyl, nitro, cyano, hydroxy,

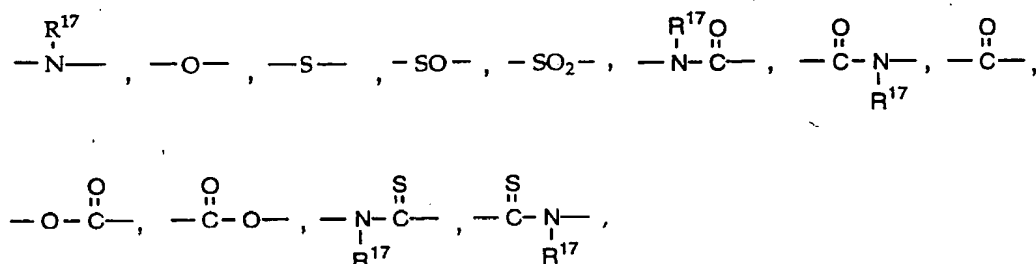
- trifluoromethyl, (C₁-C₆) alkylthio, amino, 1-3 (C₁-C₆) alkylamino, di(C₁-C₆) alkylamino, -CO₂H, -COO-(C₁-C₆) alkyl;
 -SO₃H, -SO₂NHR¹⁵ in which R¹⁵ is hydrogen or (C₁-C₆) alkyl, or

$$\begin{array}{c} \text{O} \quad \text{R}^2 \\ \parallel \quad | \\ -\text{C}-\text{N}-\text{R}^3 \end{array}$$
 in which R² and R³ are each independently hydrogen or (C₁-C₆) alkyl;
 (3) heterocyclic selected from oxadiazolyl, isoxazolyl, oxazolyl, furyl and thiazolyl;
 (4) heterocyclic substituted by one or more of, preferably 1-3, phenyl, phenyl substituted by 1-3 halo, (C₁-C₆)alkoxy, (C₁-C₆)alkyl, nitro, cyano, hydroxy, trifluoromethyl, (C₁-C₆) alkylthio, amino, (C₁-C₆) alkylamino, di(C₁-C₆) alkylamino, CO₂H, -COO-(C₁-C₆) alkyl, -SO₃H, SO₂NHR¹⁵ in which R¹⁵ is hydrogen or (C₁-C₆) alkyl, or

$$\begin{array}{c} \text{O} \quad \text{R}^2 \\ \parallel \quad | \\ -\text{C}-\text{N}-\text{R}^3 \end{array}$$
 in which R² and R³ are as defined above, (C₁-C₆) alkyl or (C₁-C₆) alkyl substituted by one or more, preferably 1-3, phenyl or heterocyclic groups, said phenyl or heterocyclic group being unsubstituted or substituted by 1-3 halo, 1-3 (C₁-C₆) alkoxy, 1-3 (C₁-C₆) alkyl, nitro, cyano, hydroxy, trifluoromethyl, (C₁-C₆) alkylthio, amino, 1-3 (C₁-C₆) alkylamino, di(C₁-C₆) alkylamino, COOH, -COO-(C₁-C₆) alkyl, -SO₃H, -SO₂NHR¹⁵ in which R¹⁵ is hydrogen or (C₁-C₆) alkyl, or

$$\begin{array}{c} \text{O} \quad \text{R}^2 \\ \parallel \quad | \\ -\text{C}-\text{N}-\text{R}^3 \end{array}$$
 in which R² and R³ are each independently hydrogen or (C₁-C₆) alkyl, the heterocyclic radical being selected from imidazolyl, oxadiazolyl, isoxazolyl, pyrrolyl, pyrazolyl, oxazolyl, furyl, thianyl or thiazolyl;
 (5) carboxy or -COO-(C₁-C₆) alkyl;
 (6) hydroxy, halo, -O-(C₁-C₆) alkyl or -S(C₁-C₆) alkyl, with the proviso that the OH, ethers or thioethers cannot be on the carbon bearing the heteroatoms;

- (7) cyano;
 (8) halogen, trifluoromethyl or trifluoroacetyl; or
 (9) $\text{CH}_2 \text{L-R}^{16}$ in which L is



5

or $-\text{O-SiR}^{16}\text{R}^{18}\text{R}^{19}$ or a bond in which R^{16} and R^{17} are each independently (C₁-C₁₈)alkyl or (C₂-C₁₈)alkenyl or (C₁-C₁₈)alkyl or (C₂-C₁₈)alkenyl substituted by one or more, preferably 1-3, phenyl or heterocyclic radicals, said phenyl or heterocyclic radicals being

10

unsubstituted or substituted by 1-5 fluoro, 1-3 halo (other than fluoro), 1-3 (C₁-C₆)alkoxy, 1-3(C₁-C₆)alkyl, nitro, cyano, hydroxy, 1-3 trifluoromethyl, 1-3 (C₁-C₆)alkylthio, amino, 1-3

(C₁-C₆)alkylamino, 1-3 di(C₁-C₆)alkylamino, CO₂H, 1-3

15

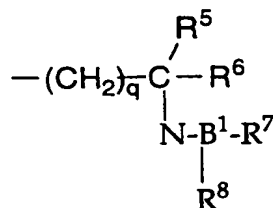
$-\text{COO}(\text{C}_1\text{-C}_6)\text{alkyl}$, $-\overset{\text{O}}{\parallel}{\text{C}}-\overset{\text{R}^2}{\text{N}}-\text{R}^3$ or $-\text{SO}_2\text{NHR}^9$ in which R^9 is hydrogen or (C₁-C₆)alkyl and R^2 and R^3 are as defined above; and R^{18} and R^{19} are phenyl or phenyl substituted by 1-3 halo, (C₁-C₆) alkoxy, (C₁-C₆) alkyl, nitro, cyano, hydroxy, trifluoromethyl, (C₁-C₆) alkylthio, amino, (C₁-C₆) alkylamino, di(C₁-C₆) alkylamino, CO₂H, -COO-

20

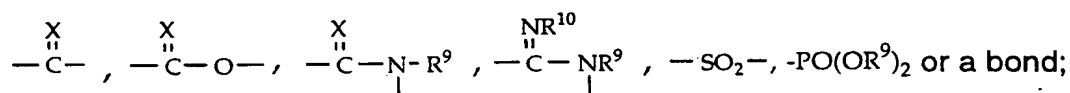
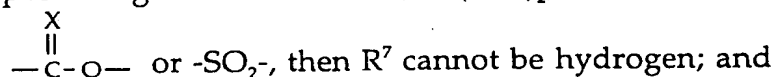
(C₁-C₆) alkyl, -SO₃H, SO₂NHR¹⁵ in which R^{15} is hydrogen or (C₁-C₆) alkyl, or $-\overset{\text{O}}{\parallel}{\text{C}}-\overset{\text{R}^2}{\text{N}}-\text{R}^3$ in which R^2 and R^3 are as defined above; or pharmaceutically acceptable salts, solvates or prodrugs thereof.

31

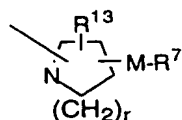
(b)

in which B¹ is

5

providing that when B¹ is -PO(OR⁹)₂, then R⁷ becomes R⁹, and when B¹ is10 X, q, R⁵, R⁶, R⁷, R⁸, R⁹ and R¹⁰ are as defined above in (a);

(c)

in which R¹³ is (C₁-C₁₈)alkyl or (C₁-C₁₈)alkyl substituted by carboxy,15 $-\overset{\text{O}}{\overset{||}{\text{C}}}-\text{O}-(\text{C}_1-\text{C}_{12}) \text{ alkyl}, -\overset{\text{O}}{\overset{||}{\text{C}}}-\overset{\text{R}^2}{\text{N}}-\text{R}^3$ in which R² and R³ are as defined above,hydroxy, -O-(C₁-C₆) alkyl, -O-(C₁-C₆) alkyl or -S-(C₁-C₆) alkyl substituted by 1 or 2 phenyl or substituted phenyl groups, the substituents for the substituted phenyl groups being 1-5 fluoro or 1-3 halo (other than fluoro),(C₁-C₆) alkoxy, (C₁-C₆) alkyl, nitro, cyano, hydroxy, trifluoromethyl, (C₁-C₆)20 alkylthio, amino, (C₁-C₆) alkylamino, di(C₁-C₆) alkylamino, CO₂H, COO-(C₁-C₆) alkyl, SO₃H, SO₂NHR¹⁵ in which R¹⁵ is hydrogen or (C₁-C₆) alkyl or

r is 0 or an integer of from 1 to 3;

R⁷ is as defined above;

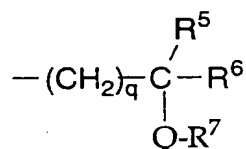
- 5 M is $-(CH_2)_mT$ where T is $-\overset{\overset{O}{\parallel}}{C}-$, $-\overset{\overset{O}{\parallel}}{C}-O$, $-\overset{\overset{O}{\parallel}}{C}-\overset{\overset{R^2}{|}}{N}-$, in which R² is as defined above, $-SO_2-$ or a bond when MR⁷ is on nitrogen and providing that when T is $-\overset{\overset{O}{\parallel}}{C}-$ or $-SO-$ or $-SO_2-$, then R⁷ cannot be hydrogen, and T is $-\overset{\overset{O}{\parallel}}{C}-$, $-\overset{\overset{O}{\parallel}}{C}-O-$, $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-\overset{\overset{R^{14}}{|}}{N}-$ or a bond when MR⁷ is on a carbon atom of the heterocyclic ring;

10

R¹⁴ is hydrogen or (C₁-C₆)alkyl;

m is 0 or an integer of 1-6;

15 (d)

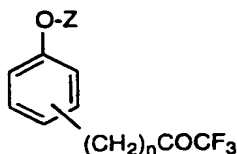


wherein Q is $-O-$, $-S-$, $-SO-$, or $-SO_2-$ and q, R⁵, R⁶ and R⁷ are as defined above, providing that when Q is $-SO-$ or $-SO_2-$, R⁷ cannot be hydrogen; or

20

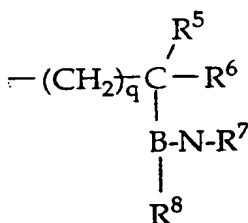
(e) R⁷ where R⁷ is as defined above, providing that when Y is $-SO-$ or $-SO_2-$, R⁷ cannot be hydrogen; or a pharmaceutically acceptable salt, solvate or prodrug thereof.

Another preferred embodiment comprises a compound of the formula



5

wherein n is 0 or an integer of from 1 to 6, the substituent $-(CH_2)_nCOCF_3$ is in the meta or para position of the phenyl ring and Z is

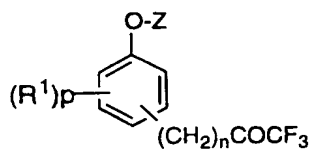


10

in which B is $\begin{array}{c} \text{X} \\ \parallel \\ -\text{C}- \end{array}$ or a bond; X is S or O; q is an integer of from 1 to 6; and R^5 , R^6 , R^7 and R^8 are as defined above; or a pharmaceutically acceptable salt, hydrate or prodrug thereof.

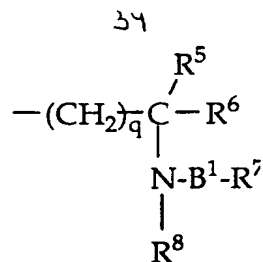
15

Another preferred embodiment comprises a compound of the formula

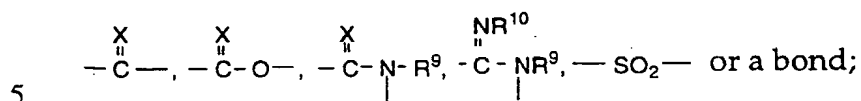


in which R^1 is benzyl; p is 0, 1 or 2; n is 0 or an integer of from 1 to 6; the substituent $-(CH_2)_nCOCF_3$ is in the meta or para position of the phenyl ring; and Z is

20



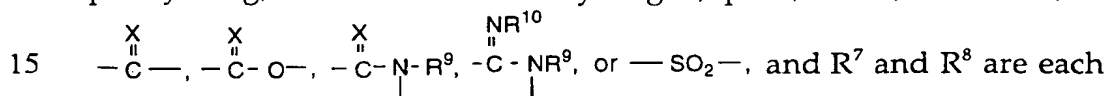
in which B¹ is



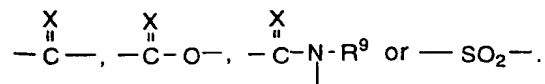
q is an integer of from 1 to 6;

X is S or O;

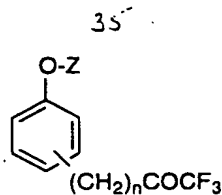
and R⁵, R⁶, R⁷, R⁸, R⁹ and R¹⁰ are as defined above; or a pharmaceutically acceptable salt, solvate or prodrug thereof. Within this embodiment, it is preferred that the substituent $-(\text{CH}_2)_n\text{COCF}_3$ is in the para position of the phenyl ring, R⁵ and R⁶ are both hydrogen, q is 1, 2 or 3, n is 2 or 3, B¹ is



independently hydrogen or (C₁-C₁₈) alkyl. Especially preferred are compounds where q is 1, n is 2 and B¹ is

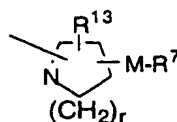


Another preferred embodiment comprises a compound of the formula



wherein n is 0 or an integer of from 1 to 6; the substituent
 $-(CH_2)_nCOCF_3$ is in the meta or para position of the phenyl ring; and Z is

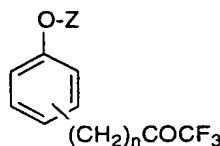
5



in which R^{13} , r, M and R^7 are as defined above, or a pharmaceutically
 acceptable salt, solvate or prodrug thereof.

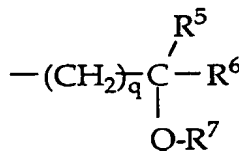
10

Another preferred embodiment comprises a compound of the
 formula



15

in which n is 0 or an integer of from 1 to 6, the substituent
 $-(CH_2)_nCOCF_3$ is in the meta or para position of the phenyl ring; and Z is

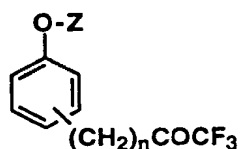


20

36

wherein q is an integer of from 1 to 6; R⁵ and R⁶ are each independently hydrogen or (C₁-C₁₈)alkyl; and Q and R⁷ are as defined above, or a pharmaceutically acceptable salt, solvate or prodrug thereof.

- 5 Another preferred embodiment comprises a compound of the formula



- 10 in which n is 0 or an integer of from 1 to 6; the substituent
 -(CH₂)_nCOCF₃ is in the meta or para position of the phenyl ring; and Z is

(a) hydrogen;

15 (b) (C₁-C₁₈)alkyl;

(c) (C₁-C₁₈)alkyl substituted by one or more, preferably 1-3, of

(1) phenyl;

20

(2) phenyl substituted by 1-5 fluoro, 1-3 halo (other than fluoro),
 1-3(C₁-C₆)alkoxy, 1-3(C₁-C₆)alkyl, nitro, cyano, hydroxy,
 trifluoromethyl, (C₁-C₆)alkylthio, amino, 1-3
 (C₁-C₆) alkylamino, di(C₁-C₆)alkylamino, -CO₂H, -COO-

(C₁-C₆)alkyl, -SO₃H, -SO₂NHR¹⁵ in which R¹⁵ is hydrogen or (C₁-C₆)alkyl, or $-\overset{\text{O}}{\underset{\text{||}}{\text{C}}}-\overset{\text{R}^2}{\underset{|}{\text{N}}}-\text{R}^3$ in which R² and R³ are each independently hydrogen or (C₁-C₆) alkyl;

- 5 (3) heterocyclic selected from oxadiazolyl, isoxazolyl, oxazolyl, furyl and thiazolyl;
- (4) heterocyclic substituted by one or more, preferably 1-3, of phenyl, phenyl substituted by 1-3 halo, (C₁-C₆)alkoxy, 10 (C₁-C₆)alkyl, nitro, cyano, hydroxy, trifluoromethyl, (C₁-C₆) alkylthio, amino, (C₁-C₆) alkylamino, di(C₁-C₆) alkylamino, CO₂H, -COO-(C₁-C₆) alkyl, -SO₃H, SO₂NHR¹⁵ in which R¹⁵ is hydrogen or (C₁-C₆) alkyl, or $-\overset{\text{O}}{\underset{\text{||}}{\text{C}}}-\overset{\text{R}^2}{\underset{|}{\text{N}}}-\text{R}^3$ in which R² and R³ are as defined above, (C₁-C₆) alkyl or 15 (C₁-C₆) alkyl substituted by one or more, preferably 1-3, phenyl or heterocyclic groups, said phenyl or heterocyclic group being unsubstituted or substituted by 1-3 halo, 1-3 (C₁-C₆) alkoxy, 1-3 (C₁-C₆) alkyl, nitro, cyano, hydroxy, trifluoromethyl, (C₁-C₆) alkylthio, amino, 1-3 (C₁-C₆) 20 alkylamino, di(C₁-C₆) alkylamino, COOH, -COO-(C₁-C₆) alkyl, -SO₃H, -SO₂NHR¹⁵ in which R¹⁵ is hydrogen or (C₁-C₆) alkyl, or $-\overset{\text{O}}{\underset{\text{||}}{\text{C}}}-\overset{\text{R}^2}{\underset{|}{\text{N}}}-\text{R}^3$ in which R² and R³ are each independently hydrogen or (C₁-C₆) alkyl, the heterocyclic radical being selected from imidazolyl, oxadiazolyl, isoxazolyl, pyrrolyl, 25 pyrazolyl, oxazolyl, furyl, thianyl or thiazolyl;
- (5) carboxy or -COO-(C₁-C₆) alkyl;

38

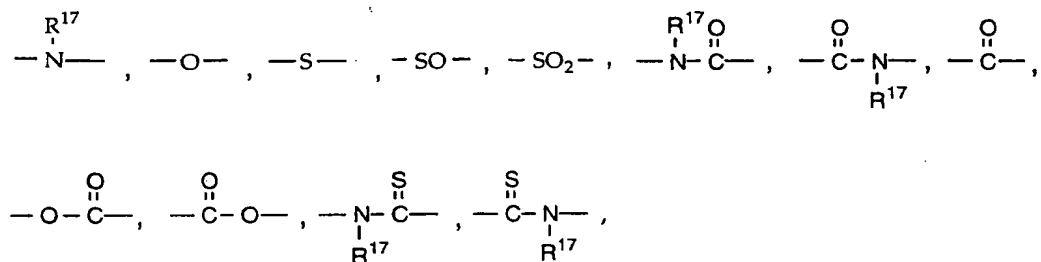
(6) hydroxy, halo, -O-(C₁-C₆) alkyl or -S-(C₁-C₆) alkyl, with the proviso that the OH, ethers or thioethers cannot be on the carbon bearing the heteroatoms;

5 (7) cyano;

(8) halogen, trifluoromethyl or trifluoroacetyl;

(9) CH₂ L-R¹⁶ in which L is

10



or -O-SiR¹⁶R¹⁸R¹⁹ or a bond in which R¹⁶ and R¹⁷ are each independently (C₁-C₁₈)alkyl or (C₂-C₁₈)alkenyl or (C₁-C₁₈)alkyl or (C₂-C₁₈)alkenyl substituted by one or more, preferably 1-3, phenyl or heterocyclic radicals, said phenyl or heterocyclic radicals being unsubstituted or substituted by 1-5 fluoro, 1-3 halo (other than fluoro), 1-3 (C₁-C₆)alkoxy, 1-3(C₁-C₆)alkyl, nitro, cyano, hydroxy, 1-3 trifluoromethyl, 1-3 (C₁-C₆)alkylthio, amino, 1-3(C₁-C₆)alkylamino,

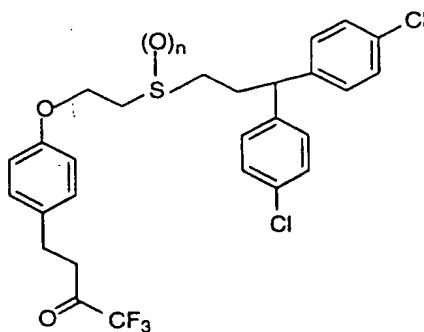
20 1-3 di(C₁-C₆)alkylamino, CO₂H, 1-3 -COO(C₁-C₆)alkyl, $-\overset{\text{O}}{\parallel}\text{C}-\overset{\text{R}^2}{\underset{\text{R}^3}{\text{N}}}-$ or -SO₂NHR⁹ in which R⁹ is hydrogen or (C₁-C₆)alkyl and R² and R³ are as defined above; and R¹⁸ and R¹⁹ are phenyl or phenyl substituted by 1-3 halo, (C₁-C₆) alkoxy, (C₁-C₆) alkyl, nitro, cyano, hydroxy, trifluoromethyl, (C₁-C₆) alkylthio, amino, (C₁-C₆) alkylamino, di(C₁-C₆)

39

alkylamino, CO_2H , $-\text{COO}-(\text{C}_1-\text{C}_6)$ alkyl, $-\text{SO}_3\text{H}$, $\text{SO}_2\text{NHR}^{15}$ in which R^{15} is hydrogen or (C_1-C_6) alkyl, or $-\text{C}(=\text{O})\text{NR}^2\text{R}^3$ in which R^2 and R^3 are as defined above; or pharmaceutically acceptable salts, solvates or prodrugs thereof.

5

Another preferred embodiment comprises a compound of the formula

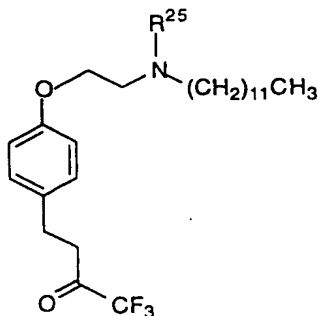


10

in which n is 0, 1 or 2; or a pharmaceutically acceptable salt or prodrug thereof.

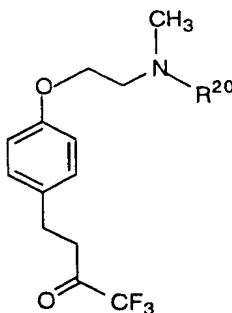
15

Preferred embodiments comprise a compound selected from those of the following



wherein

- (a) R^{25} is $-(CH_2)_3CH_3$;
 - 5 (b) R^{25} is $-(CH_2)_3CO_2C_2H_5$;
 - (c) R^{25} is $-(CH_2)_3CONHC_2H_5$;
 - (d) R^{25} is $-COCF_3$;
 - 10 (e) R^{25} is $-COC_6H_5$; and
 - (f) R^{25} is $-PO(OC_2H_5)_2$; or a pharmaceutically acceptable salt thereof.
- 15 Still other preferred embodiments comprise a compound of the formula



20 wherein

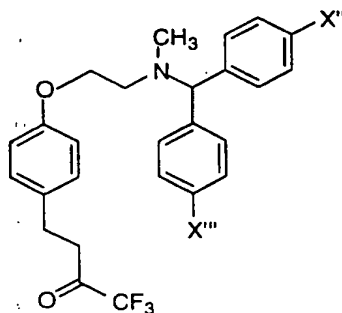
- (a) R^{20} is $-CO(CH_2)_{10}CH_3$;
- (b) R^{20} is $-COCH(p\text{-chlorophenyl})_2$; and

41

- (c) R^{20} is $-\text{SO}_2(\text{CH}_2)_{11}\text{CH}_3$; or a pharmaceutically acceptable salt thereof.

Still other preferred embodiments comprise a compound selected from those of the following

5



wherein

- 10 (a) X'' and X''' are Cl;

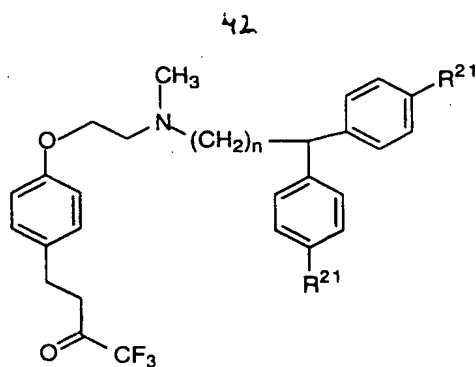
- (b) X'' and X''' are F;

- (c) X'' and X''' are OCH_3 ; and

15

- (c) X'' is Cl and X''' is OCH_3 ; or a pharmaceutically acceptable salt thereof.

Another preferred embodiment comprises a compound of the
20 formula

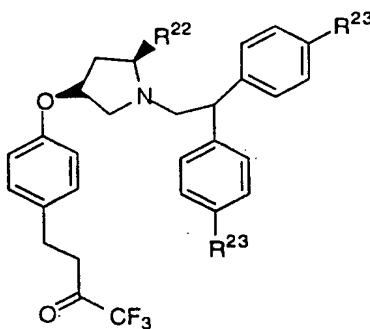


wherein

- 5 (a) n is 1 and R^{21} is OCH_3 ;
- (b) n is 1 and R^{21} is Cl ;
- (c) n is 2 and R^{21} is OCH_3 ; and
- 10 (d) n is 1-4 and R^{21} is OCH_3 or Cl ; or a pharmaceutically acceptable salt thereof.

Another preferred embodiment comprises a compound of the

15 formula

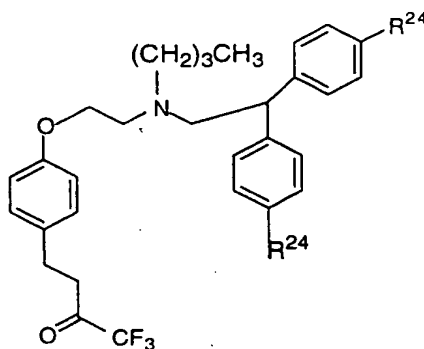


wherein

43

- (a) R^{22} is hydrogen and R^{23} is Cl; or
- (b) R^{22} is $-\text{CO}_2\text{CH}_3$ and R^{23} is $-\text{OCH}_3$; or a pharmaceutically acceptable
5 salt thereof.

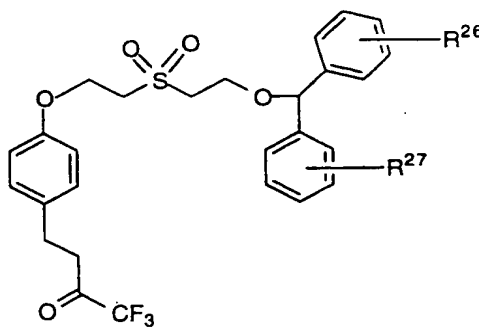
Another preferred embodiment comprises a compound of the
formula



10

wherein R^{24} is Cl or $-\text{OCH}_3$; or a pharmaceutically acceptable salt thereof.

Another preferred embodiment comprises a compound of the
15 formula



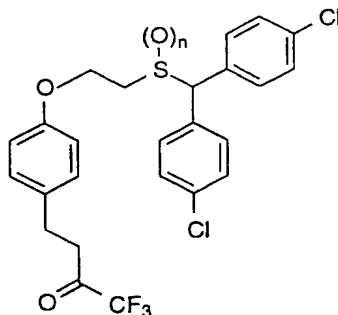
44

wherein

- (a) R^{26} and R^{27} are both CH_3 or $(\text{C}_1\text{-C}_6)\text{alkyl-CF}_3$;
- 5 (b) R^{26} and R^{27} are both Cl, F or Br;
- (c) R^{26} and R^{27} are both OCH_3 or SCH_3 ;
- (d) R^{26} is Cl and R^{27} is OCH_3 ; or
- 10 (e) R^{26} and R^{27} are both $-\text{COO}-(\text{C}_1\text{-C}_6)\text{alkyl}$; or a pharmaceutically acceptable salt thereof.

Still other preferred embodiments comprise a compound selected

15 from those of the following



20 wherein

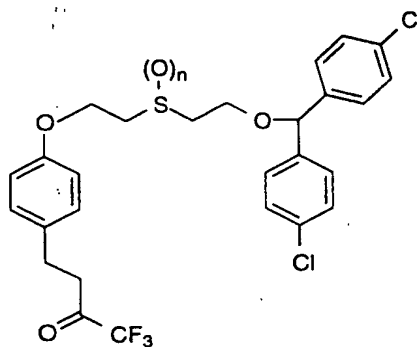
- (a) n is 0;

45

(b) $n = 1$; and

(c) $n = 2$; or a pharmaceutically acceptable salt thereof.

5 Still other preferred embodiments comprise a compound selected from those of the formula



10 wherein

(a) $n = 0$;

(b) $n = 1$; and

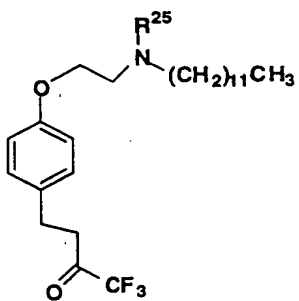
15

(c) $n = 2$; or a pharmaceutically acceptable salt thereof.

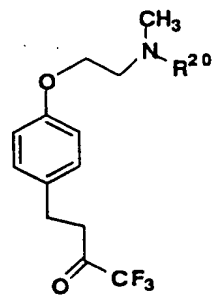
Some specific preferred embodiments of the present invention are:

20

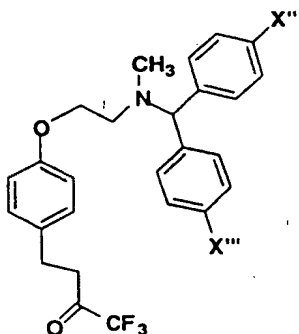
46



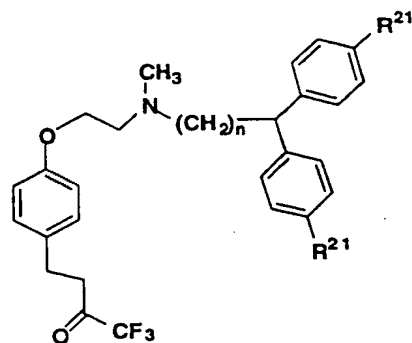
$R^{25} = (CH_2)_3CH_3$
 $R^{25} = (CH_2)_3CO_2Et$
 $R^{25} = (CH_2)_3CONHt$
 $R^{25} = COCF_3$
 $R^{25} = COC_6H_5$
 $R^{25} = PO(OEt)_2$



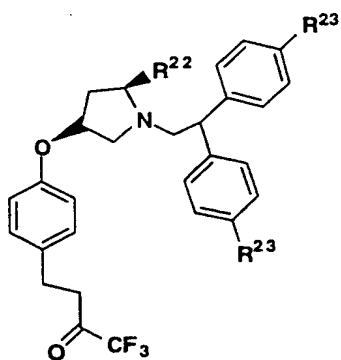
$R^{20} = CO(CH_2)_{10}CH_3$
 $R^{20} = COCH(PhCl)_2$
 $R^{20} = SO_2(CH_2)_{11}CH_3$



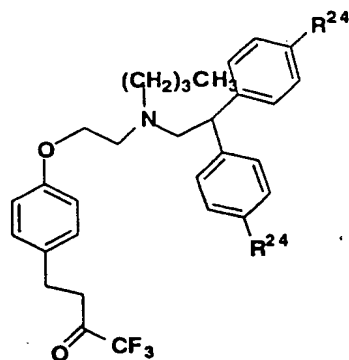
X'' and X''' are Cl
 X'' and X''' are F
 X'' and X''' are OCH_3
 X'' is Cl and X''' is OCH_3



$n = 1, R^{21} = OCH_3$
 $n = 1, R^{21} = Cl$
 $n = 2, R^{21} = OCH_3$
 $n = 1-4, R^{21} = OCH_3, Cl$

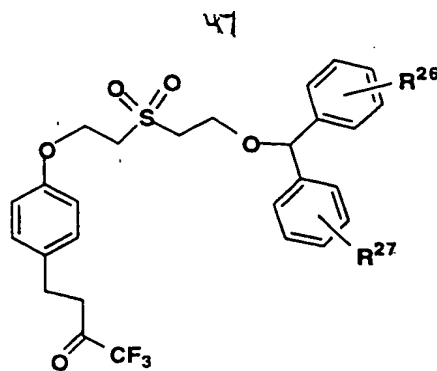


$R^{22} = H, R^{23} = Cl$
 $R^{22} = CO_2CH_3, R^{23} = OMe$



$R^{24} = Cl$
 $R^{24} = OCH_3$

and



wherein

5

(a) R^{26} and R^{27} are both CH_3 or $-(\text{C}_1\text{-C}_6)\text{alkyl-CF}_3$;

(b) R^{26} and R^{27} are both Cl, F or Br;

10 (c) R^{26} and R^{27} are both OCH_3 or SCH_3 ;

(d) R^{26} is Cl and R^{27} is OCH_3 ; or

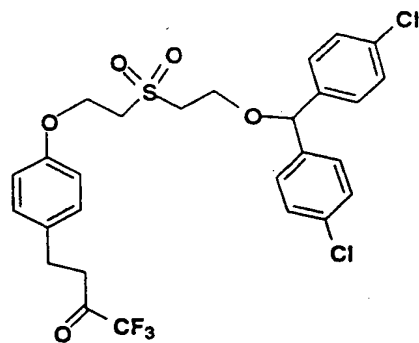
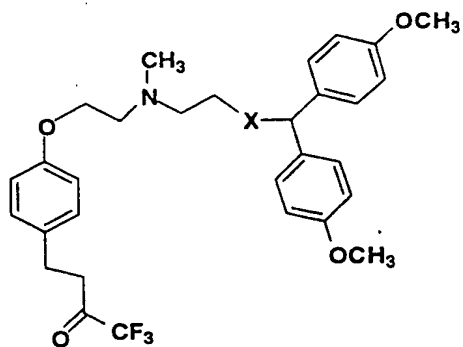
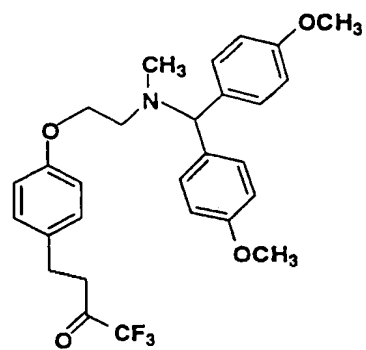
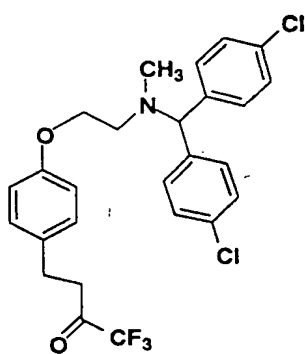
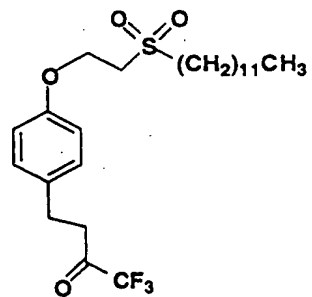
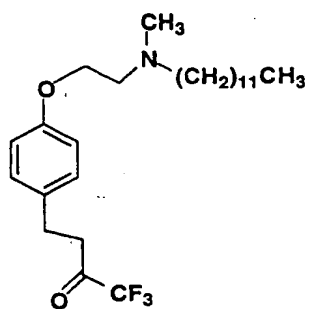
(e) R^{26} and R^{27} are both $-\text{COO}-(\text{C}_1\text{-C}_6)\text{alkyl}$.

15

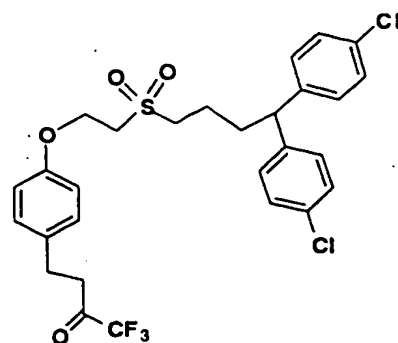
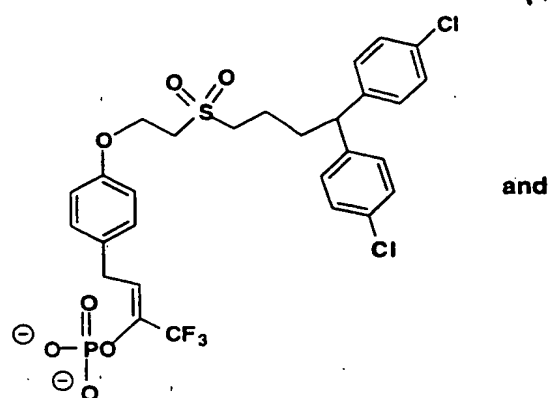
Especially preferred embodiments of the present invention include:

20

48



X = O
X = C



The compounds of the present invention can be prepared by
5 various methods which are known in the art. Illustrative methods of
preparation are provided in the reaction schemes which follow and in the
Examples.

10

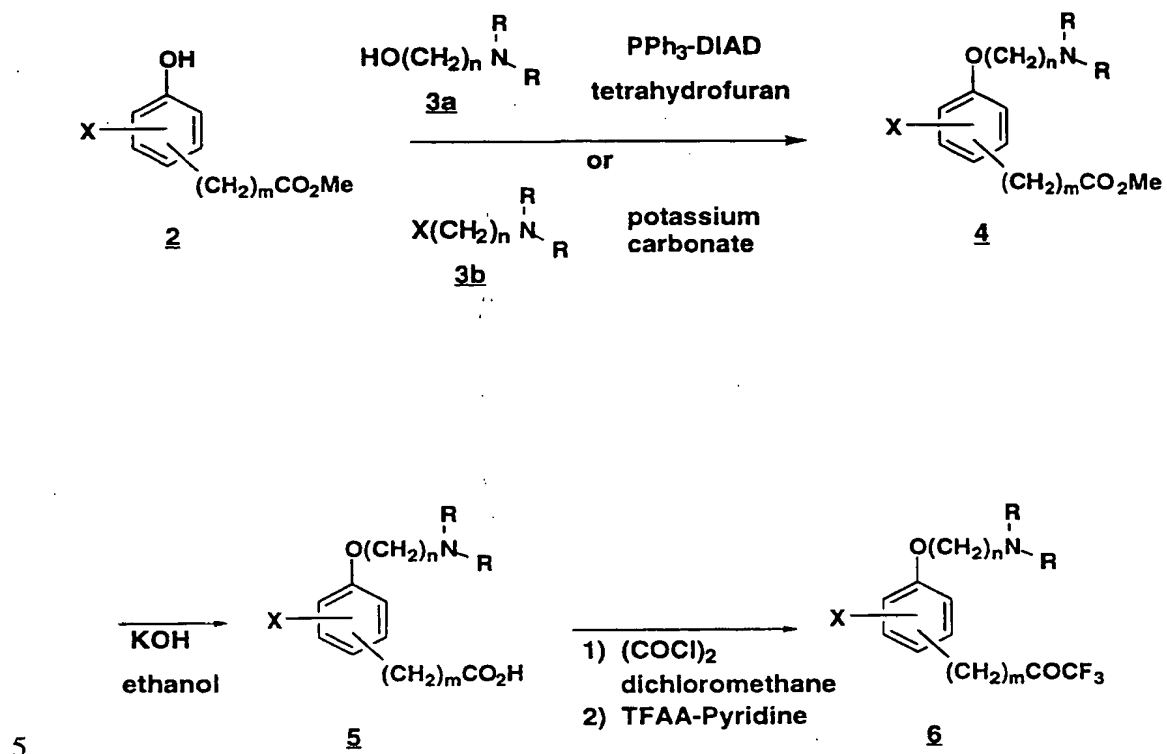
15

20

25

30

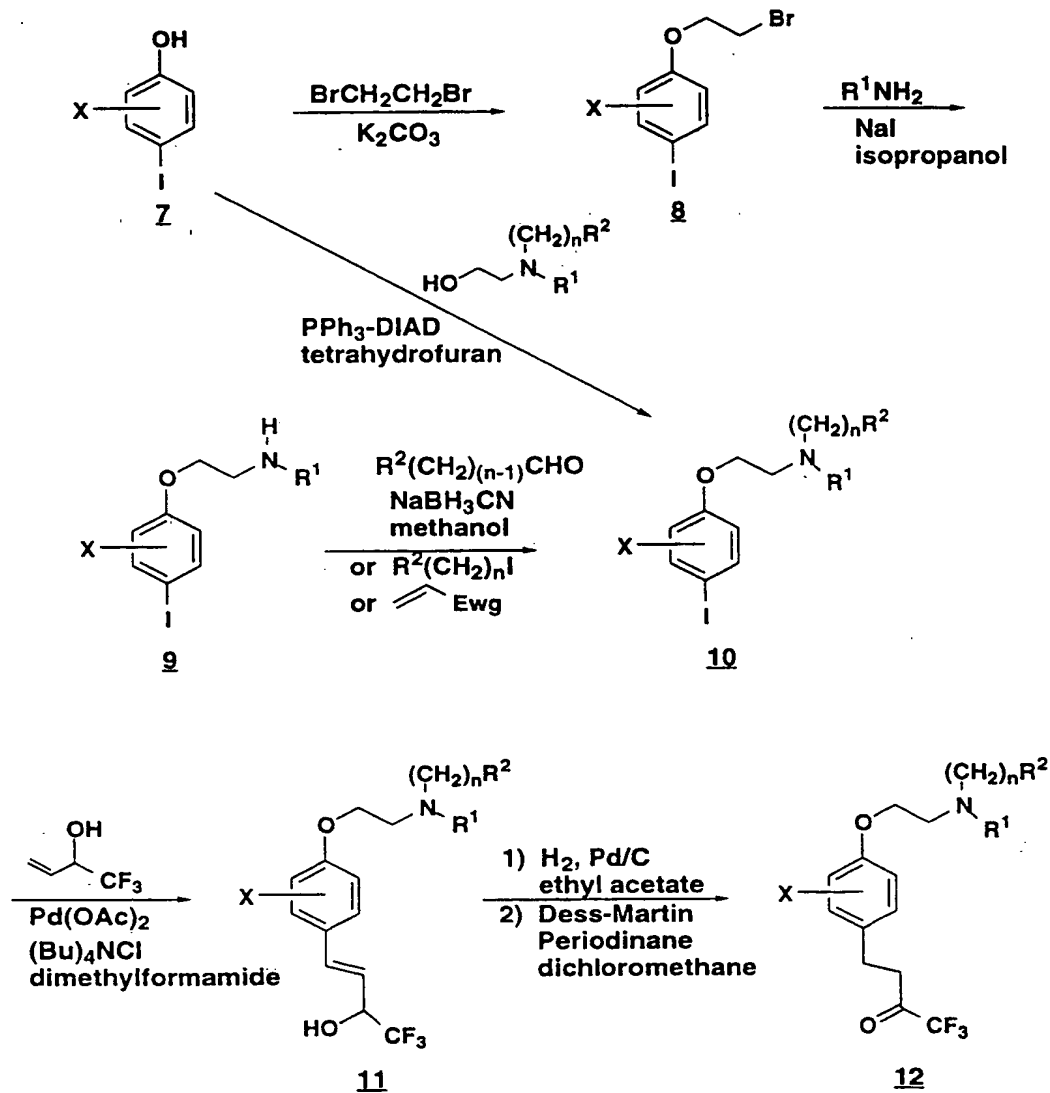
50

Scheme 1

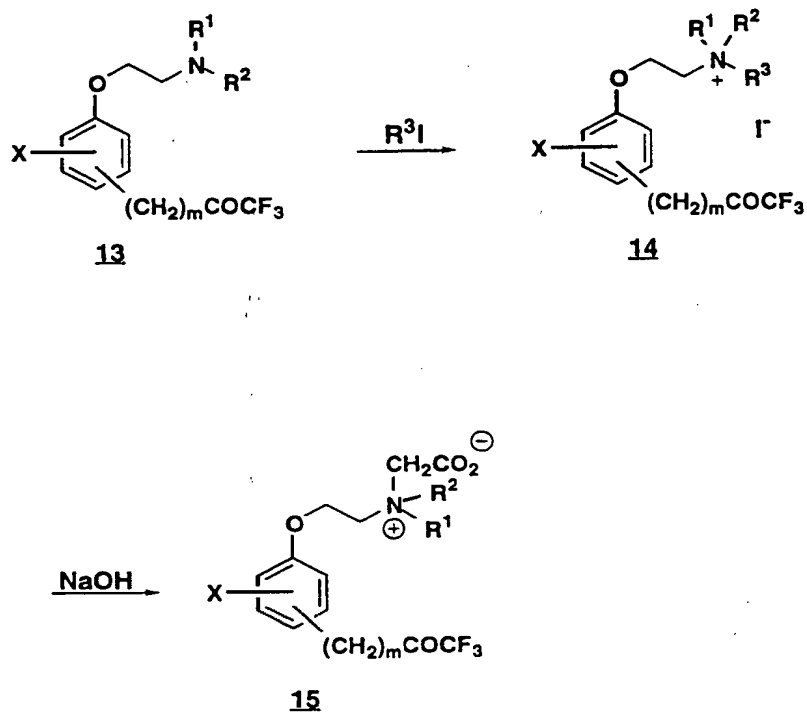
51

Scheme 2

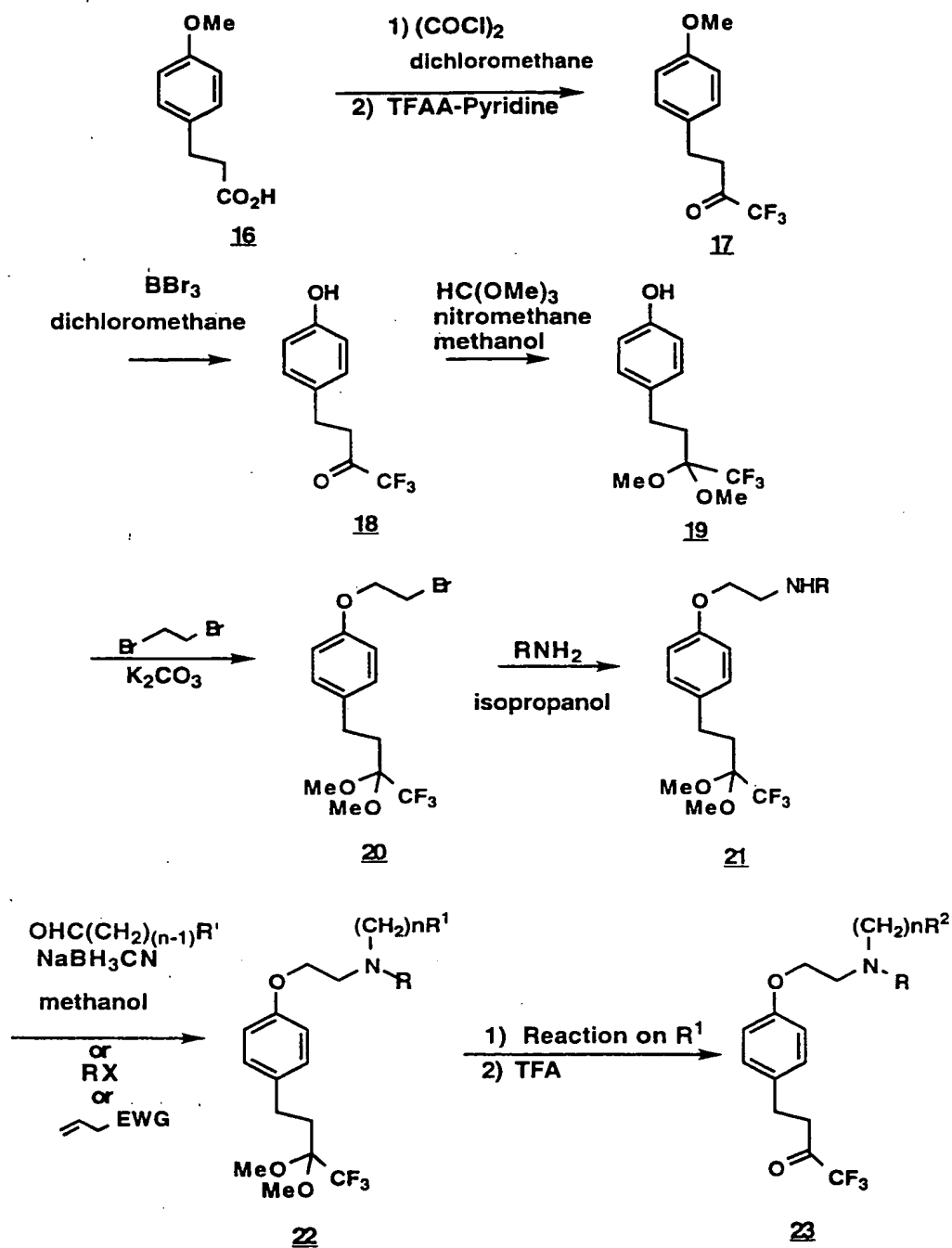
5



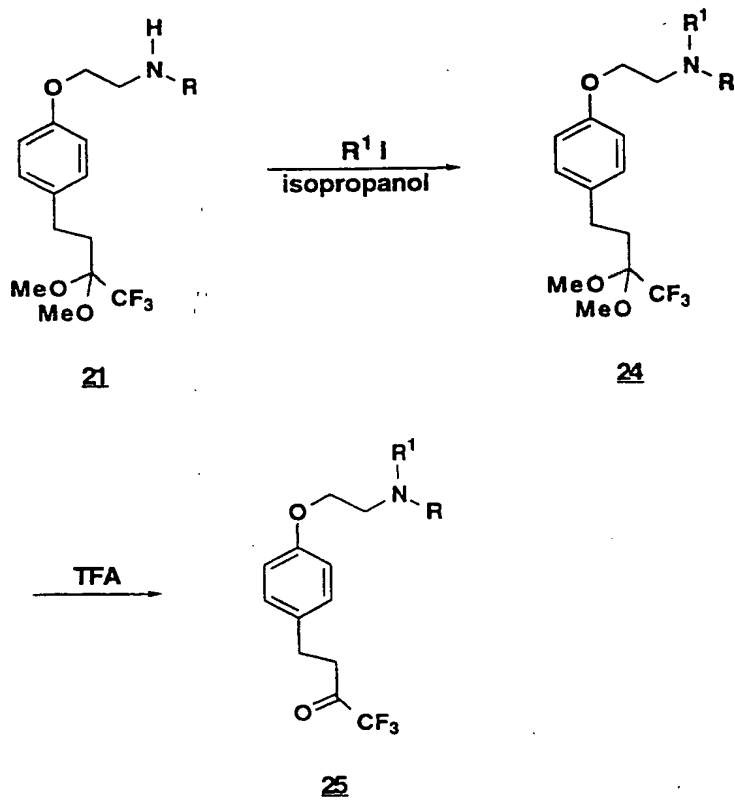
52

Scheme 3

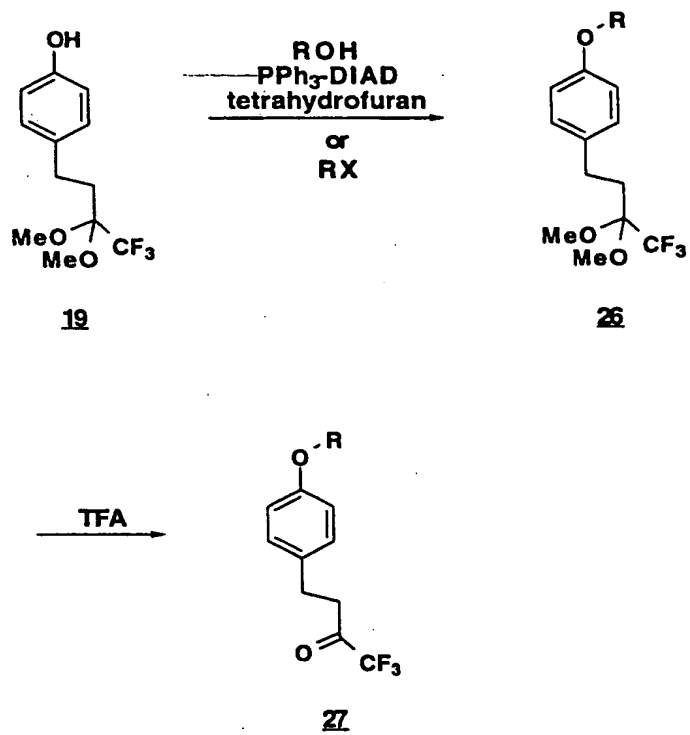
53

Scheme 4

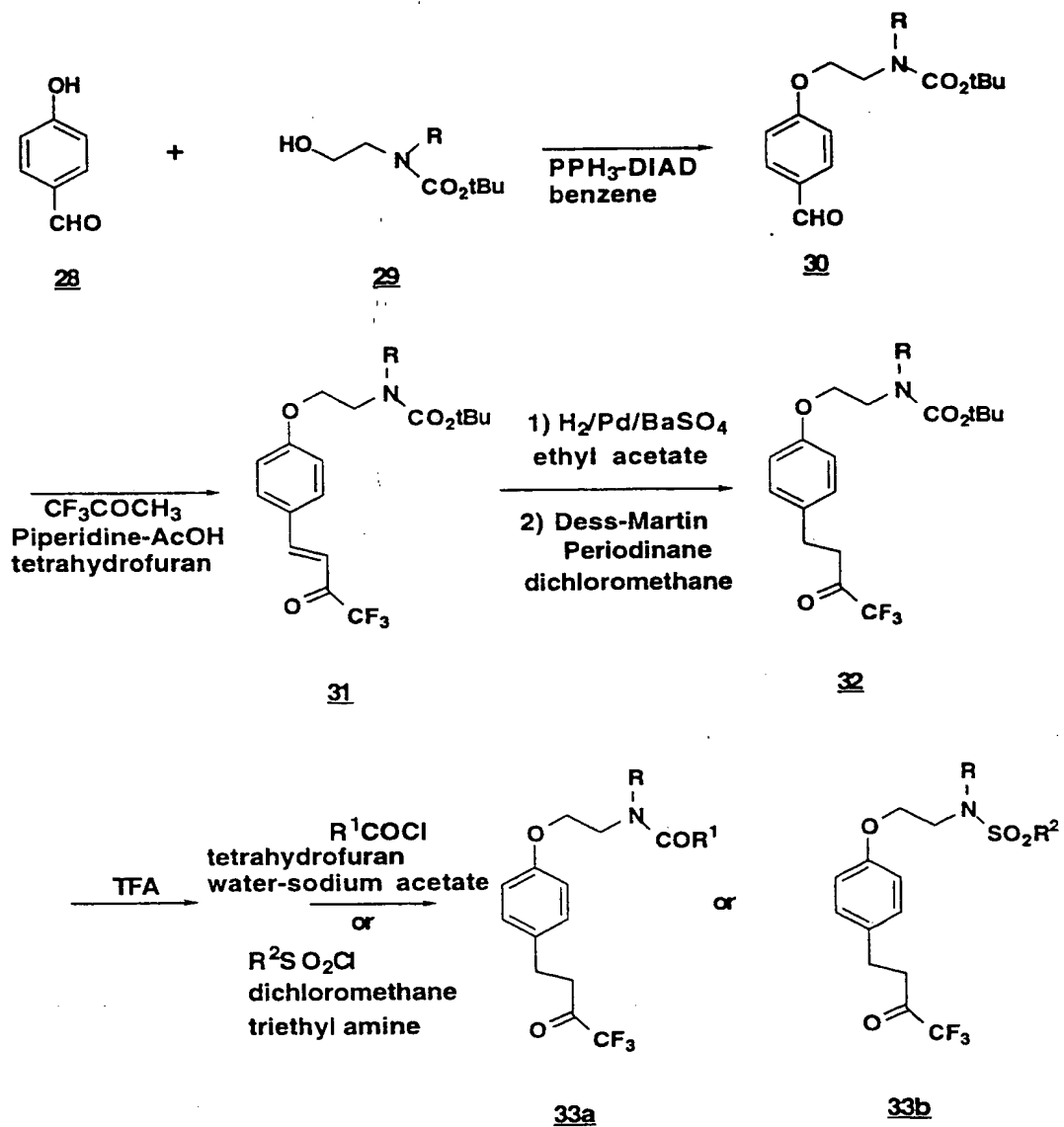
54

Scheme 5

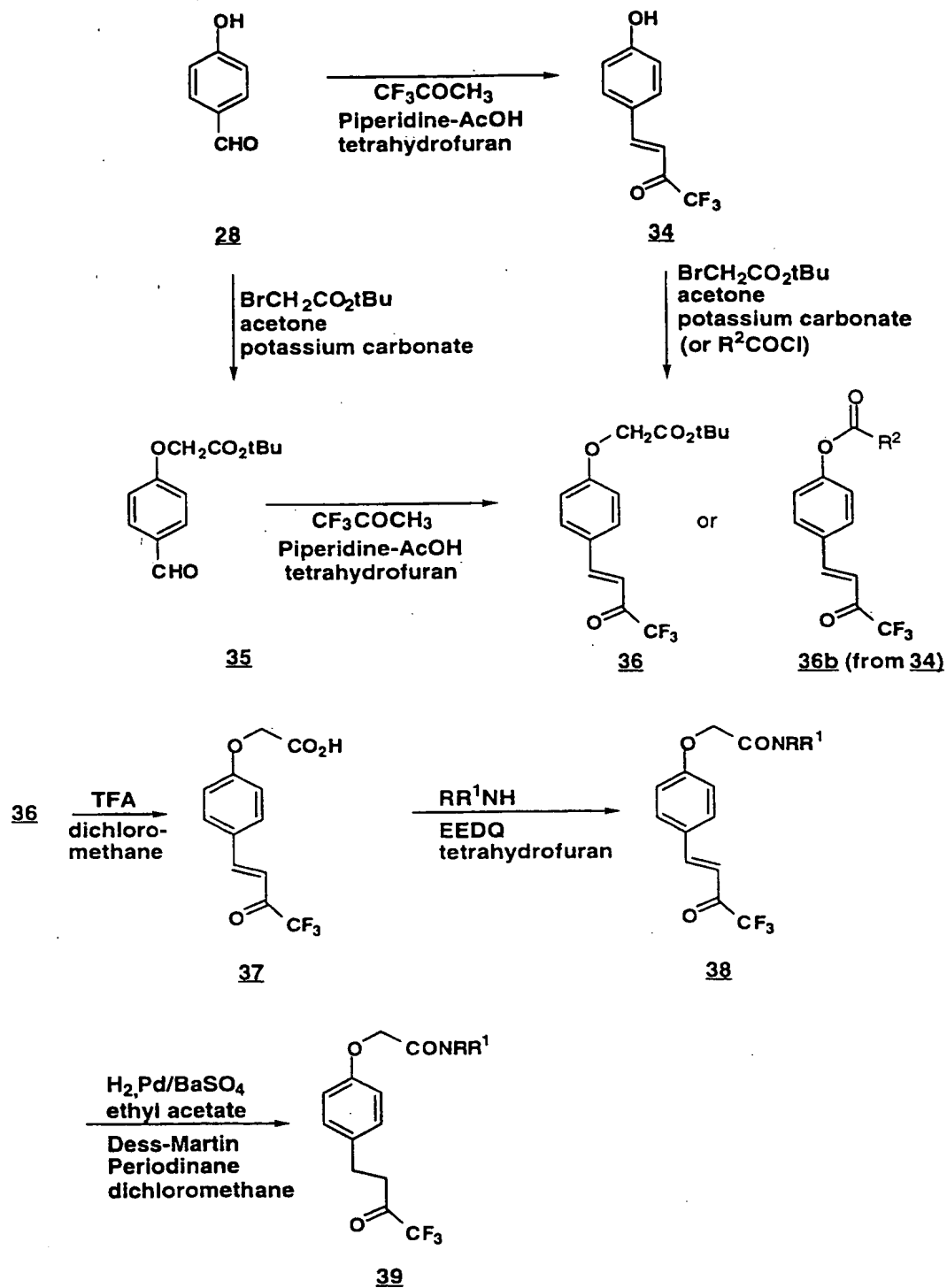
55

Scheme 6

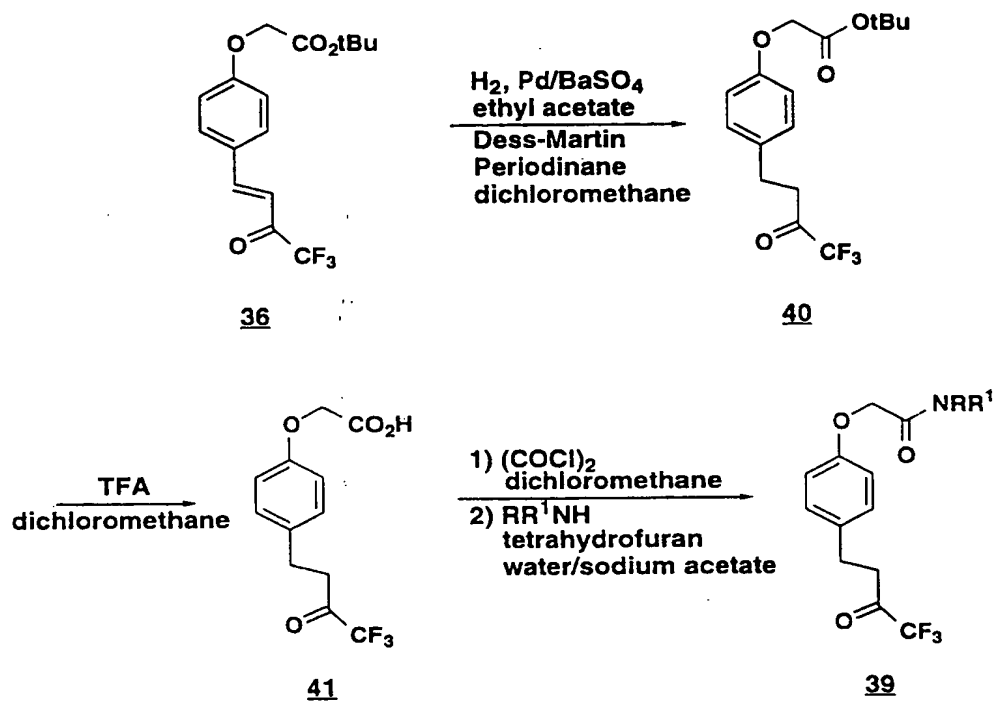
56

Scheme 7

57

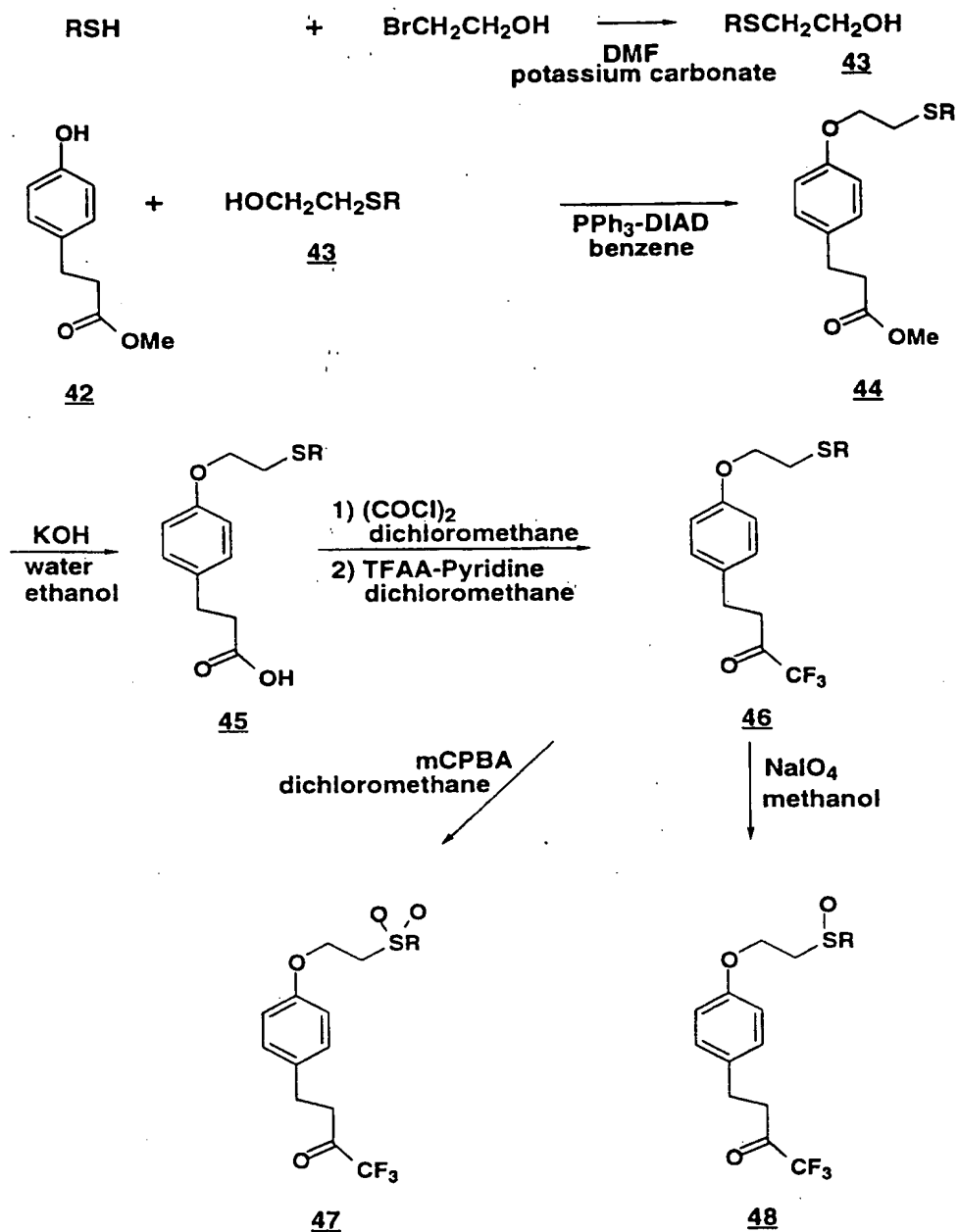
Scheme 8

58

Scheme 8 (cont.)

5

59

Scheme 9R = C₁-C₁₈ alkyl= (C₁-C₆) alkyl X(C₁-C₆) mono or bis aryl or mono or bis heterocyclesX = N-R¹O, S, SO, SO₂

Method of Preparation

Preparation of compounds of formula I may be accomplished via one or more of the synthetic schemes which are described below.

5

Scheme 1

Scheme I shows a method of preparing compounds of general structure 6. Reaction of a phenol 2 bearing a protected carboxylate group with an alcohol 3, triphenylphosphine and diethyl azodicarboxylate or diisopropyl azodicarboxylate under Mitsunobu conditions (O. Mitsunobu, Synthesis, 1, 1981) in a solvent such as tetrahydrofuran or benzene gave the ether 4. Alternatively, the phenol 2 can be alkylated with a substituted alkyl halide (RX) and a base such as potassium carbonate in a solvent such as acetonitrile or dimethylformamide to give the ether 4. The ester group of 4 is then saponified to the acid 5 by treatment with a base such as sodium hydroxide or potassium hydroxide in a solvent such as aqueous ethanol followed by neutralization with a diluted acid. The acid 5 is then treated with oxalyl chloride or thionyl chloride in a solvent such as dichloromethane to give an intermediate acid chloride. The acid chloride is then treated with trifluoroacetic anhydride and a base such as pyridine following conditions similar to those used by S.Z. Zard (Tetrahedron 51, 2573-2584, 1995) to give the trifluoromethyl ketone 6.

25 Scheme 2

Scheme 2 describes a method of preparing compounds of structure 12. Reaction of an iodo-substituted phenol 7 with a dibromo alkane of structure $\text{Br}(\text{CH}_2)_n\text{Br}$ in the presence of a base such as potassium carbonate gives 8. The bromide 8 is then displaced with a mono or disubstituted amine in the presence of sodium iodide in a solvent such as isopropanol to give 9 or 10. Alternatively, compound 10 can also be obtained under Mitsunobu conditions as described in Scheme 1. Tertiary amines 10 are also obtained by reaction of 9 with various aldehydes RCHO by reaction with a reducing agent such as sodium cyanoborohydride in a solvent such as methanol. Similar tertiary amines 10 are also prepared by

61

reaction of 2 with an iodo compound $R(CH_2)_nI$ in the presence of a base such as potassium carbonate in a solvent such as isopropanol.

- Reaction of secondary amine 2 with a Michael-type acceptor $CH_2=CH_2$ -EWG such as ethyl acrylate or acrylonitrile in a solvent such as ethanol also yields substituted amines 10. Reaction of iodophenol 10 with 4,4,4-trifluorobut-1-en-3-ol (J.A. Pegolotti and W.G. Young, J. Am. Chem. Soc., 1961, 83, 3251), under Heck-type conditions (T. Jeffery, J. Chem. Soc. Chem. Commun., 1287, 1984) in the presence of a palladium catalyst such as palladium (II) acetate in a solvent such as N,N-dimethylformamide gives the allylic alcohol 11. Hydrogenation of this allylic alcohol in the presence of a catalyst such as palladium on activated carbon in a solvent such as ethyl acetate gave an intermediate alcohol which was oxidized to the ketone 12 with the Dess-Martin periodinane (D.B. Dess and J.C. Martin, J. Org. Chem., 1983, 48, 4155) in a solvent such as dichloromethane.

Scheme 3

- Scheme 3 describes a method of preparing quaternary structures of type 14 and 15. The tertiary amine 13 is alkylated with an alkyl iodide such as methyl iodide or ethyl iodoacetate in a solvent such as isopropanol to give the quaternary amine 14. In the case where one of the R groups contains an ester group, saponification with a base such as potassium hydroxide in a solvent such as aqueous ethanol gives the zwitterionic species 15.

Scheme 4

- Scheme 4 shows a method of preparing various trifluoromethyl ketones 23 from intermediates in which the trifluoromethyl ketone is protected as a ketal group. Starting from the acid 16 which is commercially available, the trifluoromethyl ketone 17 is prepared using the method described in Scheme 1. The methyl ether 17 is then cleaved with boron tribromide in a solvent such as dichloromethane to give the phenol 18. The ketone group is then protected as a ketal 19 by reaction with an orthoester such as trimethyl orthoformate catalyzed by an acid

62

such as trifluoromethanesulfonic acid and in solvents such as nitromethane and methanol. The phenol 19 is then treated as described for Z in Scheme 2 to give 20, 21 and 22. The protected trifluoromethyl ketone in 22 allows various modifications on R¹ such as reduction of an ester group with lithium aluminum hydride or diisobutyl aluminum hydride. The ketal group is then cleaved with an acid such as trifluoroacetic acid to give 23.

Scheme 5

10

Scheme 5 describes preparation of tertiary amines by alkylation of intermediate 21 obtained in Scheme 4 by reaction with an alkyl iodide such as iodopropane in a solvent such as isopropanol and in the presence of a hindered base such as N,N-diisopropylethylamine. The ketal 24 is then cleaved as described in Scheme 4 to give the trifluoromethyl ketone 25.

Scheme 6

20 Scheme 6 describes preparation of a variety of trifluoromethyl ketones 27 starting from the phenol 19 obtained in Scheme 4. Reaction of 19 with various alcohols of structure ROH under the Mitsunobu conditions described in Scheme 1 gave 26. Deprotection of the ketal group as described in Scheme 4 gives 27 possessing a variety of ether substituents.

Scheme 7

30 Scheme 7 shows a synthetic route to acylated or sulfonylated amines 33. Reaction of 4-hydroxybenzaldehyde with a t-butoxycarbonyl-protected amino-alcohol such as 29 under Mitsunobu conditions similar to those described in Scheme 1 gives the aldehyde 30. Aldol condensation of 30 with 1,1,1-trifluoroacetone catalyzed by piperidine and acetic acid using conditions similar to those used by R.S.H. Liu (Tetrahedron Lett., 26, 2873, 1985) gave the enone 31. The enone 31 was then hydrogenated in the presence of a catalyst such as palladium on barium sulfate and treated with Dess-Martin periodinane as described in Scheme 2 to re-oxidize the

63

partially reduced carbonyl group to give 32. The t-butoxycarbonyl-protected amino derivative 32 is then treated with an acid such as trifluoroacetic acid in a solvent such as dichloromethane to give an intermediate amine as a trifluoroacetate salt. This amine is then acylated with various acyl chlorides such as palmitoyl chloride under Schotten-Baumann conditions in a mixture of solvents such as tetrahydrofuran and saturated aqueous sodium acetate to give amide 33. Alternatively, the amine trifluoroacetate salt can be treated with an alkylsulfonyl chloride such as 1-heptanesulfonyl chloride or an alkyl isothiocyanate such as N-decyl isothiocyanate in presence of a base such as triethylamine and in a solvent such as dichloromethane to give a sulfonamide or a thiourea respectively.

Scheme 8

15

Scheme 8 describes a method of preparing amides of structure 39 which are regioisomers of structures described in Scheme 7. 4-Hydroxybenzaldehyde was treated with 1,1,1-trifluoroacetone as described in Scheme 7 and alkylated with a bromoester such as t-butyl bromoacetate in the presence of a base such as potassium carbonate and in a solvent such as acetone to give 36. Alternatively 36 can be obtained via the same sequence of steps but in inverse order. The phenol 34 can also be acylated with various acid chlorides such as a palmitoyl chloride to give ester derivatives such as 36b. The t-butyl protecting group of 36 is then cleaved with an acid such as trifluoroacetic acid in dichloromethane to give the acid 37. This acid is then reacted with primary and secondary amines such as dodecylamine in the presence of a condensing agent such as N-ethoxycarbonyl-2-ethoxy-1,2-dihydroxyquinoline (EEDQ) to give the amide 38. Reduction and oxidation of the enone as described in Scheme 7 gave the amide 39. Alternatively, the enone 36 can be reduced first to 40 and then cleaved as above to the acid 41. The acid 41 is then treated with oxalyl chloride in dichloromethane to give an intermediate acid chloride. Reaction of this acid chloride with primary and secondary amines such as p-chlorobenzhydrylamine hydrochloride in a mixture of tetrahydrofuran and saturated aqueous sodium acetate also gives amides of structure 39.

35

Scheme 9

Scheme 2 describes a method for making compounds of structure 46, 47 and 48 which contain a sulfur atom. Reaction of an alcohol 43 which contains a sulfur atom, usually obtained by reaction of a thiol with a halogen-substituted alcohol, with phenol 42 under Mitsunobu conditions as described in Scheme 1 gives the ether 44. Preparation of the trifluoromethylketone 46 is then achieved via the two-step sequence also described in Scheme 1. Oxidation of 46 with a peracid such as m-chloroperbenzoic acid gives the sulfone 47. Oxidation of 46 with sodium periodate in a mixture of methanol and water affords the sulfoxide 48.

Biological Activity

Assay for determining activity as cPLA₂ inhibitors:

15

³H-arachidonate-labeled U937 membranes were prepared from U937 cells grown in RPMI 1640 medium containing L-glutamine supplemented with 10% fetal calf serum and 50 µg/ml gentamycin in a 5% CO₂ incubator at 37°C. Sixteen hours prior to harvesting the cells, ³H-arachidonate (100 Ci/mmol) was added to the cell culture (1x10⁶ cells/ml, 0.5 µCi/ml). After washing the cells with HBSS (Hank's Balanced Salts) containing 1 mg/ml HSA (Human Serum Albumin), the cells were lysed by nitrogen cavitation and the homogenate was centrifuged at 2,000x g for 10 minutes. The supernatant was further centrifuged at 50,000x g for 30 minutes after which the pellet was resuspended in water and autoclaved at 120°C for 15 minutes to inactivate any residual phospholipase A₂ activity. This suspension was then recentrifuged at 50,000x g for 30 minutes and the pellet resuspended in distilled water.

30

Assays of cPLA₂ activity using these ³H-arachidonate-labeled U937 membranes as substrate typically employ human recombinant cPLA₂ (see

65

Burke et al., Biochemistry 34: 15165-15174, 1995) and membrane substrate (22 μ m phospholipid) in 20 mM HEPES [N-(2-hydroxyethyl)piperazine-N¹-(2-ethanesulfonic acid)] buffer, pH 8, containing 6 mM CaCl₂, 0.9 mg/ml albumin and 4 mM glycerol. Enzyme assays are allowed to proceed for 3
5 hours at 37°C before removing the non-hydrolyzed membranes. The hydrolyzed, radiolabeled fatty acid is then measured by liquid scintillation counting of the aqueous phase.

The effects of inhibitor are calculated as percent inhibition of ³H-arachidonate formation, after correcting for nonenzymatic hydrolysis, as
10 compared to a control lacking inhibitor according to the following formula:

$$\text{percent inhibition} = ((\text{Control DPM} - \text{Inhibitor DPM}) / \text{Control DPM}) \\ 15 \times 100\%$$

Various concentrations of an inhibitor were tested, and the percent inhibition at each concentration was plotted as log concentration (abscissa) versus percent inhibition (ordinate) to determine the IC₅₀ values.
20

In this assay the compounds of Examples 1-274 below exhibited cPLA₂ IC₅₀ values in the range of from about 1 to 50 μ m.

Since the compounds of the present invention are selective
25 inhibitors of cytosolic phospholipase A₂, they are of value in the treatment of a wide variety of clinical conditions.

Inflammatory disorders which may be treated by inhibition of cytosolic cPLA₂ include such conditions as arthritis, psoriasis, asthma, inflammatory bowel disease, gout, trauma-induced inflammation such as spinal cord injury, Alzheimer's Disease, cerebral ischemia, chronic skin inflammation, shock, damage to skin resulting from exposure to ultraviolet light or burns, allergic rhinitis, acute pancreatitis, and the like.

The compounds of formula I are usually administered in the form of pharmaceutical compositions. They can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. The compounds are effective as both injectable and oral compositions. Such compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound defined by formula I and a pharmaceutically acceptable carrier.

In making the compositions employed in the present invention the active ingredient is usually mixed with an excipient, diluted by an excipient or enclosed within a carrier which can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be a solid, semisolid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing for example up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

In preparing a formulation, it may be necessary to mill the active compound to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it ordinarily is milled to a particle size of less than 200 mesh. If
5 the active compound is substantially water soluble, the particle size is normally adjusted by milling to provide a substantially uniform distribution in the formulation, e.g. about 40 mesh.

Some examples of suitable excipients include lactose, dextrose,
10 sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and
15 suspending agents; preserving agents such as methyl- and propylhydroxybenzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

20

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 5 to about 100 mg, more usually about 10 to about 30 mg, of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human
25 subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

68

The active compound is effective over a wide dosage range. For example, dosages per day normally fall within the range of about 0.5 to about 30 mg/kg of body weight. In the treatment of adult humans, the range of about 1 to about 15 mg/kg/day, in single or divided dose, is especially preferred. However, it will be understood that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way. In some instances dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, provided that such larger doses are first divided into several smaller doses for administration throughout the day.

SPECIFIC EXAMPLES

The following examples further illustrate the preparation of the compounds of formula I. The examples are illustrative only and are not intended to limit the scope of the invention in any way. The following abbreviations have the indicated meanings:

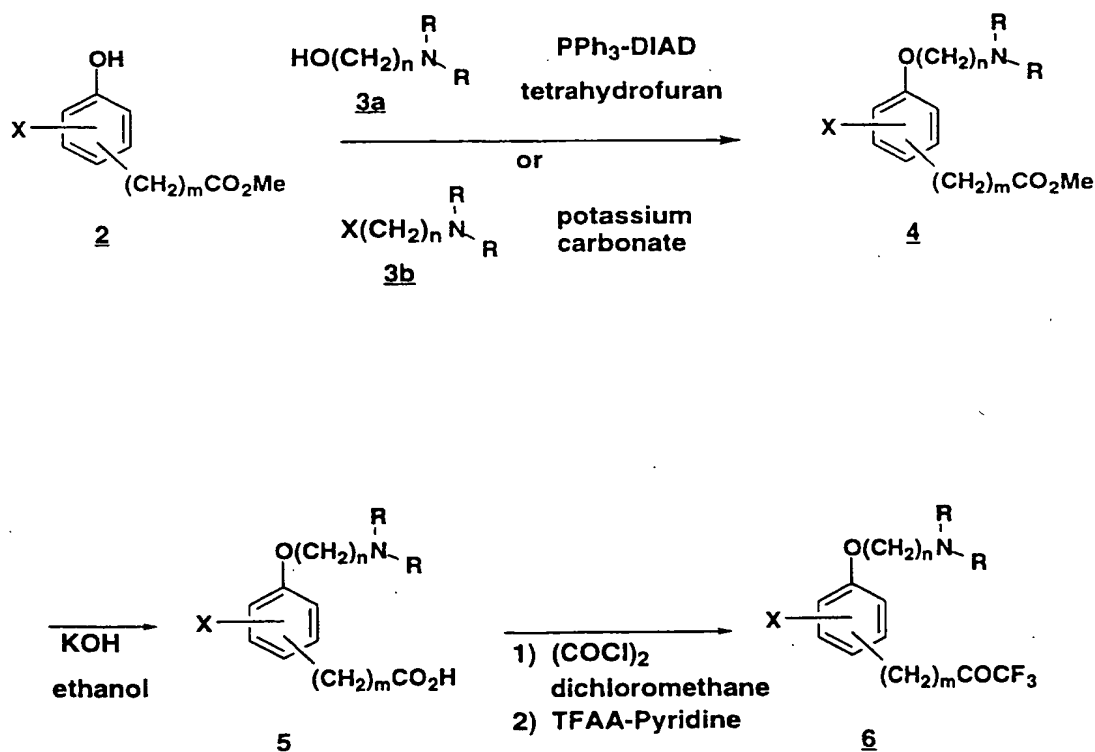
AcOH	acetic acid
EWG	electron-withdrawing groups
DIAD	diisopropyl azodicarboxylate
TFAA	trifluoroacetic anhydride

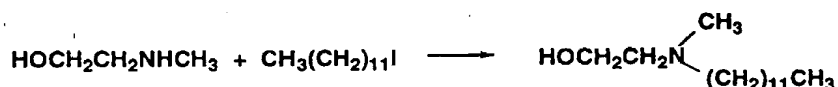
69

	r.t.	room temperature
	THF	tetrahydrofuran
	TFA	trifluoroacetic acid
5	EEDQ	N-ethoxycarbonyl-2-ethoxy-1,2-dihydroxyquinoline
	DMF	N,N-dimethylformamide
	DEAD	diethyl azodicarboxylate
	CPBA	m-chloroperbenzoic acid
	Me	CH ₃
10	Ph	phenyl
	tBu	tert-butyl

Scheme 1

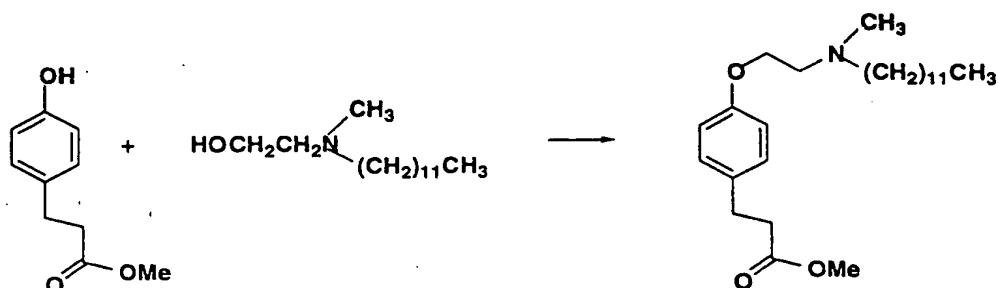
15



Example 1**4-[4-[2-(N-Dodecyl-N-methylamino)ethoxy]phenyl]1,1,1-trifluoro-2-butanone****5 N-Methyl-N-Dodecylethanolamine**

- A solution of iodododecane (18.1 g, 61.09 mmol) and 2-
- 10 (methylamino)ethanol (23.0 g, 0.3 mol) in isopropanol (75 ml) was heated under reflux for 3 h. The cooled mixture was diluted with ether (500 ml), washed with water, brine and dried (magnesium sulfate). Evaporation of the solvent under reduced pressure and distillation of the residue under vacuum gave 14.5 g (97%) of N-methyl-N-dodecylethanolamine as a clear
- 15 oil: b.p. 100-111°C/0.3 torr (bulb to bulb distillation, air bath temperature). IR (NaCl, film) ν_{max} (cm^{-1}) 3400 (OH). ^1H NMR 400 MHz (CDCl_3) δ (ppm): 0.89 (3H, t, $J=5.36$ Hz, CH_3), 1.1-1.5 (20H, br m, $(\text{CH}_2)_{10}$), 2.24 (3H, s, NCH_3), 2.39 (2H, t, $J=7.4$ Hz, NCH_2), 2.52 (2H, t, $J=5.35$ Hz, $\text{OCH}_2\text{CH}_2\text{N}$), 3.58 (2H, t, $J=5.35$ Hz, $\text{OCH}_2\text{CH}_2\text{N}$).

3-[4-[2-(N-Dodecyl-N-methylamino)ethoxy]phenyl]propanoic acid methyl ester



5

- A solution of methyl 3-(4-hydroxyphenyl)propionate (10.0 g, 55.5 mmol), N-methyl-N-dodecylethanolamine (13.5 g, 55.5 mmol) and triphenylphosphine (16.0 g, 61.0 mmol) in dry tetrahydrofuran (200 ml) was treated at 22°C with diisopropyl azodicarboxylate (12.3 g, 61.0 mmol) added dropwise over 50 min. After 3 h at 22°C, the reaction mixture was evaporated under reduced pressure and the residue was triturated with hexane. The solid formed was filtered, washed with hexane and the combined filtrate was chromatographed on silica gel using a gradient of ethyl acetate in hexane (20% - 60%) as eluent. Distillation under vacuum then gave 18.0 g (75%) of 3-[4-[2-(N-dodecyl-N-methylamino)ethoxy]phenyl] propanoic acid, methyl ester as a clear oil: b.p. 180-183°C/0.02 torr (bulb to bulb distillation, air bath temperature). ¹H NMR 400 MHz (CDCl₃) δ (ppm): 0.89 (3H, t, J=6.8 Hz, CH₃), 1.2-1.6 (20H, m, CH₂)₁₀), 2.33 (3H, s, NCH₃), 2.43 (2H, t, J=7.6 Hz, NCH₂), 2.60 (2H, t, J=7.77 Hz, CH₂-2), 2.78 (2H, t, J=6.06 Hz, OCH₂CH₂N), 2.89 (2H, t, J=7.77 Hz, CH₂-3), 3.67 (3H, s, OCH₃), 4.04 (2H, t, J=6.06 Hz, OCH₂CH₂N), 6.84 (2H, d, J=8.55 Hz, aromatic), 7.11 (2H, d, J=8.55 Hz, aromatic).
- The hydrochloride salt was obtained by treating the amine with anhydrous hydrochloric acid (1M) in ether:

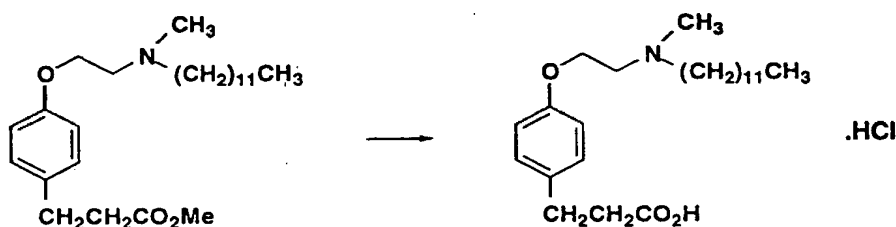
72

Anal. Calcd. for $C_{25}H_{43}NO_3 \cdot HCl$: C 67.92, H 10.03, N 3.17.

Found: C 67.74, H 9.46, N 3.25.

3-[4-[2-(N-Dodecyl)-N-methylamino]ethoxy]phenyl]-propanoic acid.

5 hydrochloride salt.



A solution of 3-[4-[2-(N-dodecyl)-N-methylamino]ethoxy]phenyl]propanoic
 10 acid methyl ester (2.30 g, 5.69 mmol) in ethanol (25 ml) was treated with
 potassium hydroxide (0.64 g, 11.4 mmol) and water (5 ml) and stirred at 22°C
 for 2 h. The reaction mixture was then acidified to pH 4 with 1M
 hydrochloric acid and extracted twice with ethyl acetate. The combined
 extracts were washed with brine, dried ($MgSO_4$) and evaporated under
 15 reduced pressure to give a white solid. Recrystallization from ethyl acetate
 gave 2.20 g (89%) of 3-[4-[2-(N-dodecyl)-N-

methylamino]ethoxy]phenyl]propanoic acid as white crystals.

IR (KBr) ν_{max} (cm^{-1}): 1725 (C=O of carboxylate).

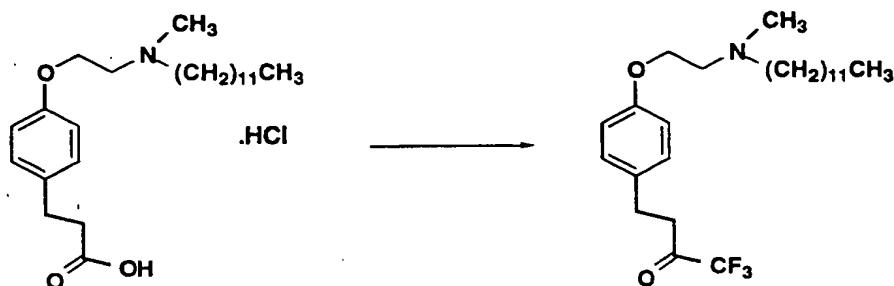
1H NMR 400 MHz ($CDCl_3$) δ (ppm): 0.89 (3H, t, $J=6.8$ Hz, $-CH_3$), 1.2-1.4
 20 (18H, br m, $(CH_2)_9$), 1.87 (2H, m, NCH_2CH_2), 2.61 (2H, t, $J=7.5$ Hz, CH_2-2),
 2.87 (3H, s, NCH_3), 2.88 (2H, t, $J=7.5$ Hz, CH_2-3), 3.11 (2H, br t, NCH_2CH_2),
 3.44 (2H, br t, OCH_2CH_2N), 4.41 (2H, br t, OCH_2CH_2N), 6.81 (2.11, d, $J=8.58$
 Hz, aromatic), 8.56 (2H, d, $J=8.58$ Hz, aromatic).

Anal. Calcd. for $C_{24}H_{41}NO \cdot HCl$: C 67.34, H 9.89, N 3.27.

25 Found: C 67.08, H 9.82, N 3.18.

73

4-[4-[2-(N-Dodecyl-N-methylamino)ethoxy]phenyl]1,1,1-trifluoro-2-
butanone



5

A solution of 3-[4-[2-(N-dodecyl-N-methylamino)ethoxy]phenyl]propanoic acid hydrochloride salt (3.30 g, 7.71 mmol) in dry dichloromethane (35 ml) was treated with oxalyl chloride (1.61 g, 12.7 mmol) and a small drop of N,N-dimethylformamide. After 1 h at 22°C, the solvent and excess reagent were

10 evaporated under reduced pressure and the residue was dissolved in dry dichloromethane (35 ml). This solution was then added to a solution of trifluoroacetic anhydride (5.31 g, 24.2 mmol) in dry dichloromethane (30 ml) cooled to 0°C and treated dropwise with pyridine (1.4 ml, 17.3 mmol). After stirring for 30 min at 0°C and another 1.5 h at 22°C, the reaction mixture was

15 cooled again to 0°C and treated dropwise with water (13 ml). After 30 min at 0°C and another 30 min at 22°C, the reaction mixture was adjusted to pH 8-9 with solid sodium bicarbonate and diluted with dichloromethane (200 ml). The organic phase was then washed with brine and dried (magnesium sulfate). The solvent was evaporated under reduced pressure and the

20 residual oil was chromatographed on silica gel. Elution with a gradient of ethyl acetate in hexane gave an oil which was distilled under vacuum to give 2.45 g (71%) of 4-[4-[2-(N-dodecyl-N-methylamino)ethoxy]phenyl]1,1,1-trifluoro-2-butanone as a clear oil: b.p. 160°C/0.02 torr (bulb to bulb distillation, air bath temperature).

14

IR (NaCl, film) ν_{max} (cm^{-1}) : 1760 (C=O).

^1H NMR 400 MHz (CDCl_3) δ (ppm) : 0.89 (3H, t, $J=6.8$ Hz, $-\text{CH}_3$), 1.1-1.6 (20H, m, $(\text{CH}_2)_{10}$), 2.32 (3H, s, NCH_3), 2.44 (2H, t, $J=7.6$ Hz, NCH_2), 2.79 (2H, t, $J=6.0$ Hz, $\text{OCH}_2\text{CH}_2\text{N}$), 2.94 and 3.0 (2 x 2H, 2m, CH_2 -3 and 4), 4.06 (2H, t, $J=6.0$ Hz, $\text{OCH}_2\text{CH}_2\text{N}$), 6.86 (2H, d, $J=8.6$ Hz, aromatic), 7.10 (2H, d, $J=8.6$ Hz, aromatic).

Anal. Calcd. for $\text{C}_{25}\text{H}_{40}\text{F}_3\text{NO}_2 \cdot 0.6 \text{H}_2\text{O}$: C 68.08, H 9.09, N 3.16.

Found: C 68.08, H 9.19, N 3.11.

The hydrochloride salt was obtained by treating the amine with anhydrous hydrochloric acid (1M) in ether.

Anal. Calcd. for $\text{C}_{25}\text{H}_{40}\text{F}_3\text{NO}_2 \cdot \text{HCl} \cdot 1.1 \text{H}_2\text{O}$: C 60.07, H 8.71, N 2.80.

Found: C 59.99, H 8.62, N 2.98.

Example 2

4-[4-[3-(N-Dodecyl-N-methylamino)propoxy]phenyl]-1,1,1-trifluoro-2-butanone

3-(N-dodecyl-N-methylamino)propanol

A solution of 3-(methylamino)propanol (5.71 g, 64.0 mmol, S. Koepke, R. Kupper, and C.J. Michejda, J. Org. Chem., 44, 2718, 1979), and iodododecane (7.58 g, 25.6 mmol) was reacted as described in example 1 to give 6.33 g (96%) of the title material as an oil, b.p. 100-105°C/0.04 torr.

75

3-[4-[3-(N-dodecyl-N-methylamino)propoxy]phenyl]propanoic acid,
methyl ester.

Methyl 3-(4-hydroxyphenyl)propanoate (1.0 g, 5.5 mmol) and 3-(N-
5 dodecyl-N-methylamino)propanol (1.43 g, 5.5 mmol) were reacted as
described in example 1 to give 1.57 g (43%) of title material as an oil.
Anal. Calcd. for C₂₆H₄₅NO₃: C 74.42, H 10.81, N 3.34.
Found: C 74.02, H 10.54, N 3.49.

10 3-[4-[3-(N-Dodecyl-N-methylamino)propoxy]phenyl]propanoic acid,
hydrochloride

3-[4-[3-(N-dodecyl-N-methylamino)propoxy]phenyl]propanoic acid,
methyl ester (1.53 g, mmol) was reacted as described in example 1 to give
15 1.20 g (74%) of the starting material as an amorphous solid.
Anal. Calcd. for C₂₆H₄₅NO₃: C 74.42, H 10.81, N 3.34.
Found: C 74.02, H 10.54, N 3.49.

20 4-[4-[3-(N-Dodecyl-N-methylamino)propoxy]phenyl]1,1,1-trifluoro-2-
butanone

3-[4-[3-(N-dodecyl-N-methylamino)propoxy]phenyl]propanoic acid,
hydrochloride (0.45 g, 1.11 mmol) was reacted as described in example 1 to
give 0.185 g (36%) of the title material as an oil, b.p. 140-160°C/0.04 torr
25 (bulb to bulb distillation, air bath temperature).
Anal. Calcd. for C₂₆H₄₂F₃NO₂·0.2H₂O: C 67.71, H 9.27, N 3.04.
Found: C 67.75, H 9.35, N 2.90.
The hydrochloride was obtained as a syrup.

76

Example 3**4-[4-[4-(N-Dodecyl-N-methylamino)butoxy]phenyl]1,1,1-trifluoro-2-butanone**

5

Methyl 3-[4-(4-bromobutoxy)phenyl]propanoate

A mixture of methyl 3-(4-hydroxyphenyl) propionate (1.19 g, 6.6 mmol), 1,4-dibromobutane (10 g, 46.3 mmol) and powdered anhydrous potassium carbonate (2.3 g) was maintained at 80°C and stirred vigorously for 24 h. Alter cooling, the solid was filtered and washed with a mixture of hexane and ethyl acetate (4:1). The filtrate was concentrated under reduced pressure and the residue was chromatographed on silica gel. Elution with a gradient of ethyl acetate (0-3%) in toluene gave 1.80 g (86%) of the title material as an oil.

10

15

Anal. Calcd. for C₁₄H₁₉BrO₃: C 53.25, H 6.08.

Found: C 53.24, H 5.74.

3-[4-[4-(N-Dodecyl-N-methylamino)butoxy]phenyl]-propanoic acid, methyl ester

20

A mixture of methyl 3-(4-bromobutoxy)phenyl]propanoate (1.46 g, 4.63 mmol), N-methyldodecylamine (2.31 g, 11.6 mmol) and sodium iodide (50 mg) in acetonitrile (17 ml) was heated at 75°C for 3 h. The reaction mixture was then cooled, diluted with dichloromethane, washed with saturated sodium bicarbonate, brine and dried over anhydrous magnesium sulfate. The solvent was then evaporated under reduced pressure and the residue was chromatographed on silica gel. Elution with

25

a gradient of methanol (0 - 5%) in ether gave 1.69 g (85%) of the title material as an oil.

Anal. Calcd. for $C_{27}H_{47}NO_3$: C 79.48, H 10.92, N 3.23.

Found: C 74.62, H 10.58, N 3.25.

5

3-[4-[4-(N-Dodecyl-N-methylamino)butoxy]phenyl]-propanoic acid, hydrochloride

3-[4-[4-N-dodecyl-N-methylamino)butoxy]phenyl]propanoic acid, methyl ester (0.800 g, 1.84 mmol) was saponified as described in example 1 to give 0.778 g (93%) of the title material as white crystals after crystallization from ethyl acetate; m.p. 109 - 111°C.

Anal. Calcd. for $C_{26}H_{45}NO_3 \cdot HCl$: C 68.47, H 10.17, N 3.07.

Found: C 68.49, H 9.92, N 3.07.

15

4-[4-[4-(N-Dodecyl-N-methylamino)butoxy]phenyl]-1,1,1-trifluoro-2-butanone

3-[4-[4-(N-dodecyl-N-methylamino)butoxy]phenyl]-propanoic acid, hydrochloride (0.740 g, 1.76 mmol) was reacted as described in example 1 to give 0.420 g (51%) of the title material as an oil: b.p. 150 - 180°C/0.025 torr (bulb to bulb distillation, air bath temperature).

Anal. Calcd. for $C_{27}H_{44}F_3NO_2$: C 68.76, H 9.40.

Found: C 68.52, H 9.38.

25

The hydrochloride was obtained as a syrup.

Anal. Calcd. for $C_{27}H_{44}F_3NO_2 \cdot HCl \cdot 0.5 H_2O$: C 62.71, H 8.97, N 2.71.

Found: C 62.69, H 8.71, N 2.76.

Example 4**12-[2-(N-Dodecyl-N-methylamino)ethoxy]phenyl]-2,2,2-trifluoroethanone**

- 5 2-Trifluoroacetylphenol (Matsumoto, S. ; Kobayashi, H. and Ueno, K. *Bull.Chem. Soc. Jpn.* 1969, 42, 960) (490mg, 2.57mmol) and 2-[N-dodecyl-N-methylamino] ethanol (627mg, 2.58mmol) were reacted by the general procedure as described in example 1 and afforded the title compound
- 10 (654mg, 61%) as a pale yellow oil.
Analysis for $C_{23}H_{36}F_3NO_2 \cdot 0.3H_2O$ calcd. C 65.63%, H 8.76%, N 3.33%;
Found: C 65.44%, H 8.74%, N 3.48%.
Treatment of the above free amine with anhydrous hydrogen chloride (1.0 M in ether) gave the hydrochloride salt as a white waxy solid.
- 15 Analysis for $C_{23}H_{36}F_3NO_2 \cdot HCl \cdot 0.5H_2O$ calcd. C 59.92%, H 8.31%, N 3.04%;
Found: C 59.67%, H 8.49%, N 3.16%.

Example 5

- 20 **4-[4-[2-(N-Dodecyl-N-methylamino)ethoxy]-2-methoxyphenyl]-1,1,1-trifluoro-2-butanone**

7-[2-(N-Dodecyl-N-methylamino)ethoxy]-2H-1-benzopyran-2-one

- 25 7-Hydroxycoumarin (6.0g, 37.0mmol) and 2-[N-dodecyl-N-methylamino] ethanol (9.0g, 37.0mmol) were reacted by the general procedure as described in example 1 and afforded the title compound (6.7g, 47%) as a white solid.
Analysis for $C_{24}H_{37}NO_3$ calcd C 74.38%, H 9.62%, N 3.61%; Found:
- 30 74.35%, H 9.45%, N 3.66%.

7-[2-(N-Dodecyl-N-methylamino)ethoxy]-3,4-dihydro-2H-1-benzopyran-2-one

- 35 7-[2-(N-Dodecyl-N-methylamino)ethoxy]-2H-1-benzopyran-2-one (5.62g, 14.5mmol) in ethyl acetate was hydrogenated over palladium on activated carbon under 30 psi and afforded the title compound (4.7g, 84%) as a white solid.

76

Treatment of the above free amine with anhydrous hydrogen chloride (1.0 M in ether) gave the hydrochloride salt as a white solid.

Analysis for $C_{24}H_{39}N O_3 \cdot HCl \cdot 0.7H_2O$ calcd. C 65.72%, H 9.51%, N 3.19%;

Found: C 65.76% H 9.35% N 3.26%.

5

3-[4-[2-(N-Dodecyl-N-methylamino)ethoxy]-2-hydroxyphenyl]propanoic acid, methyl ester

A solution of 7-[2-(N-Dodecyl-N-methylamino)ethoxy]-3,4-dihydro-2H-1-benzopyran-2-one (2.0g, 5.13mmol) in methanol (30ml) was stirred at 22°C
10 for 0.5h. The solvent was then removed *in vacuo* at 40°C to afford the title compound (2.14g, 100%) as a white solid.

3-[4-[2-(N-Dodecyl-N-methylamino)ethoxy]-2-methoxyphenyl]propanoic acid, methyl ester
15

3-[4-[2-(N-Dodecyl-N-methylamino)ethoxy]-2-hydroxyphenyl]propanoic acid, methyl ester (500mg, 1.18mmol) and methanol (0.096ml, 2.37mmol) were reacted under Mitsunobu conditions as described in example 1 and
20 afforded the title compound (471mg, 81%) as a pale yellow oil.

3-[4-[2-(N-Dodecyl-N-methylamino)ethoxy]-2-methoxyphenyl]propanoic acid, hydrochloride

3-[4-[2-(N-Dodecyl-N-methylamino)ethoxy]-2-methoxyphenyl]propanoic acid, methyl ester (468mg, 1.07mmol) was saponified as described in the preparation of 3-[4-[2-(N-dodecyl-N-methylamino)ethoxy]phenyl]propanoic acid, hydrochloride and afforded
25 the title compound (280mg, 62%) as a white solid.

30 Analysis for $C_{25}H_{43}NO_4$ calcd. C 64.60%, H 9.46%, N 3.01%; Found: C 64.69%, H 9.52%, N 3.22%.

4-[4-[2-(N-Dodecyl-N-methylamino)ethoxy]-2-methoxyphenyl]-1,1,1-trifluoro-2-butanone

35

3-[4-[2-(N-Dodecyl-N-methylamino)ethoxy]-2-methoxyphenyl]propanoic acid, hydrochloride (274mg, 0.598mmol) was reacted by the general

80

procedure as described in the preparation of 4-[4-[2-(N-dodecyl-N-methylamino)-ethoxy]phenyl]-1,1,1-trifluoro-2-butanone and afforded the title compound (165mg, 58%) as a pale yellow oil (b.p. 138-140°C/0.015mmHg).

- 5 Treatment of the above free amine with anhydrous hydrogen chloride (1.0 M in ether) gave the hydrochloride salt as a off-white sticky solid. Analysis for $C_{26}H_{42}F_3NO_3 \cdot HCl \cdot 0.7H_2O$ calcd. C 58.80%, H 8.76%, N 2.74%; Found: C 58.89%, H 8.53%, N 2.64%.

10 Example 6

7-[2-(N-Dodecyl-N-methylamino)ethoxy]-3,4-dihydro-2-(trifluoromethyl)-2H-1-benzopyran-2-ol

- 15 A mixture of 4-[4-[2-(N-dodecyl-N-methylamino)ethoxy]-2-methoxyphenyl]-1,1,1-trifluoro-2-butanone (157mg, 0.33mmol) and hydrobromic acid (47%, 3ml) was refluxed for 3.5h. After cooling to r.t., the mixture was diluted with water, extracted with dichloromethane. The organic layer was washed with sat. sodium bicarbonate, brine, dried over
20 magnesium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel (ethyl acetate/acetone 3 : 1) to afford the title compound (60mg, 40%) as a clear oil.
Treatment of the above free amine with anhydrous hydrogen chloride (1.0 M in ether) gave the hydrochloride salt as a off-white sticky solid.
25 Analysis for $C_{25}H_{40}F_3NO_3 \cdot HCl \cdot 0.3H_2O$ calcd. C 59.88%, H 8.36%, N 2.79%; Found: C 59.84%, H 8.29%, N 2.79%.

Example 7

- 30 4-[4-[2-(N-Dodecyl-N-methylamino)ethoxy]-2-vinylphenyl]-1,1,1-trifluoro-2-butanone

3-[4-[2-(N-Dodecyl-N-methylamino)ethoxy]-2-[trifluoromethanesulfonyloxy]phenyl]propanoic acid, methyl ester

35

To a solution of 3-[4-[2-(N-dodecyl-N-methylamino)ethoxy]-2-hydroxyphenyl]propanoic acid, methyl ester (2.53g, 6.0mmol) and dry pyridine (1.94ml, 24.0mmol) in dichloromethane (30ml) at 0°C was added dropwise trifluoromethanesulfonic anhydride (2.1ml, 12.0mmol). After stirring for 20h at 22°C, the mixture was diluted with ethyl acetate (120ml), washed with water (3x50ml), brine (50ml), dried over magnesium sulfate and concentrated *in vacuo*. The residue was placed at 0°C and triturated with diethyl ether. The formed solid (trifluoromethanesulfonic acid salt of the title compound) was dissolved in dichloromethane, washed with sat. sodium bicarbonate, brine and dried over magnesium sulfate. The solvent was removed *in vacuo* to afford the title compound (2.15g, 69%) as a brown oil which solidified upon standing.

15 3-[4-[2-(N-Dodecyl-N-methylamino)ethoxy]-2-vinylphenyl]propanoic acid, methyl ester

To a solution of 3-[4-[2-(N-dodecyl-N-methylamino)ethoxy]-2-[trifluoromethanesulfonyloxy]-phenyl]propanoic acid, methyl ester (250mg, 0.48mmol) in 1,4-dioxane (2.5ml) were added tributylvinyltin (1.2ml, 4.0mmol), lithium chloride (123mg, 1.44mmol), tetrakis(triphenylphosphine)-palladium(0) (10mg) and 2,6-di-*tert*-butyl-4-methylphenol (10mg). The resulting mixture was then stirred at 100°C for 5h. After cooling to r.t., the mixture was diluted with diethyl ether, washed with water, brine, dried over magnesium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel (diethyl ether/acetone 100 : 0 to 80 : 20) to afford the title compound (170mg, 80%) as a yellow oil.

30 3-[4-[2-(N-Dodecyl-N-methylamino)ethoxy]-2-vinylphenyl]propanoic acid, hydrochloride

3-[4-[2-(N-Dodecyl-N-methylamino)ethoxy]-2-vinylphenyl]propanoic acid, methyl ester (178mg, 0.412mmol) was saponified as described in the preparation of 3-[4-[2-(N-dodecyl-N-methylamino)ethoxy]phenyl]propanoic acid, hydrochloride and afforded the title compound (175mg, 93%) as a clear oil.

4-[4-[2-(N-Dodecyl-N-methylamino)ethoxy]-2-vinylphenyl]-1,1,1-trifluoro-2-butanone

- 3-[4-[2-(N-Dodecyl-N-methylamino)ethoxy]-2-vinylphenyl]propanoic acid, hydrochloride (830mg, 1.83mmol) was reacted by the general procedure as described in the preparation of 4-[4-[2-(N-dodecyl-N-methylamino)-ethoxy]phenyl]-1,1,1-trifluoro-2-butanone. The residue was chromatographed on silica gel (ethyl acetate) to afford the title compound (0.46g, 54%) as a pale purple oil.
- 10 Analysis for $C_{27}H_{42}F_3NO_2 \cdot 0.5H_2O$ calcd. C 67.75%, H 9.06%, N 2.93%; Found: C 67.85%, H 8.92%, N 2.90%.
- Treatment of the above free amine with anhydrous hydrogen chloride (1.0 M in ether) gave the hydrochloride salt as a pale green sticky solid.
- Analysis for $C_{27}H_{42}F_3NO_2 \cdot HCl \cdot 1.3H_2O$ calcd. C 61.24%, H 8.68%, N 2.65%;
- 15 Found: C 61.07%, H 8.42%, N 2.63%.

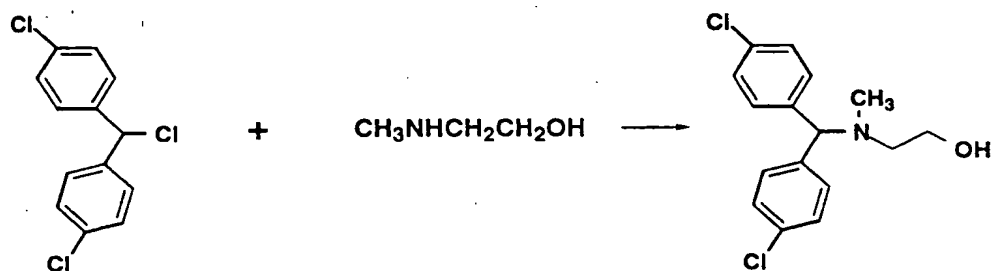
Example 8

20 8-[2-(N-Dodecyl-N-methylamino)ethoxy]-3-hydroxy-1-(hydroxymethyl)-3-(trifluoromethyl)-1,3,4,5-tetrahydro-2-benzoxepin

- A solution of 4-methylmorpholine N-oxide (31mg, 0.23mmol) and osmium tetroxide (1mg, 0.004mmol) in acetone (1ml) and water (2.5ml) was treated with 4-[4-[2-(N-dodecyl-N-methylamino)ethoxy]-2-
- 25 vinylphenyl]-1,1,1-trifluoro-2-butanone (100mg, 0.21mmol) dissolved in tert-butanol (1ml). After stirring at 22°C for 16h, the mixture was treated with aqueous sodium bisulfite (20%, 5ml) and extracted with diethyl ether. The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. The residue was
- 30 chromatographed on silica gel (diethyl ether/acetone 80 : 20 to 50 :50) to afford the title compound (40mg, 39%) as a clear oil.
- Treatment of the above free amine with anhydrous hydrogen chloride (1.0 M in ether) gave the hydrochloride salt as an off-white solid.
- Analysis for $C_{27}H_{44}F_3NO_4 \cdot HCl \cdot 0.7H_2O$ calcd. C 58.67%, H 8.46%, N 2.53%;
- 35 Found: C 58.67%, H 8.18%, N 2.45%.

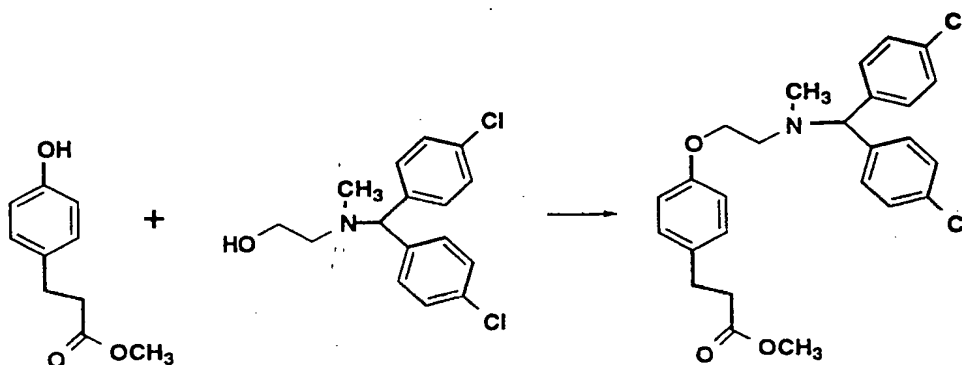
Example 9**4-[4-[2-[N-[Bis-(4-chlorophenyl)methyl]N-methylamino]ethoxy]phenyl]-1,1,1-trifluoro-2-butanone.**

5

2-[N-[Bis-(4-chlorophenyl)methyl]N-methylamino]ethanol

- 10 A solution of 4,4'-dichlorobenzhydryl chloride (5.20 g, 19.1 mmol) and 2-(methylamino)ethanol (9.0 g, 0.106 mol) in acetonitrile (100 ml) was treated with powdered anhydrous potassium carbonate (10 g) and the resulting mixture was heated under reflux for 4 h. The cooled mixture was filtered and the filtrate was concentrated *in vacuo*. The residual oil
- 15 was diluted with ethyl acetate, washed with water and brine and then dried over anhydrous magnesium sulfate. Evaporation of the solvent *in vacuo* followed by chromatography on silica gel (elution toluene-ethyl acetate 9:1) gave 4.29 g (79%) of the title material as a white solid: mp 49-50°C.
- 20 Anal. Calcd. for $C_{16}H_{17}Cl_2NO$: C 61.95, H 5.52, N 4.52.
Found: C 61.58, H 5.43, N 4.61.

3-[4-[2-[N-[Bis-(4-chlorophenyl)methyl]-N-methylamino]ethoxy]phenyl]-propanoic acid methyl ester.



5

A solution of methyl 3-[4-hydroxyphenyl]propanoate (0.594 g, 3.3 mmol) and 2-[N-[bis-(4-chlorophenyl)methyl]-N-methylamino]ethanol and triphenylphosphine (0.952 g, 3.63 mmol) in tetrahydrofuran (12 ml) was treated dropwise at 22°C with diisopropyl azodicarboxylate (0.734 g, 3.63 mmol). After 3 h, the solvent was evaporated *in vacuo* and the residue was chromatographed on silica gel (elution hexane-ethyl acetate 83:17) to give 1.12 g (72%) of the title material as an oil.

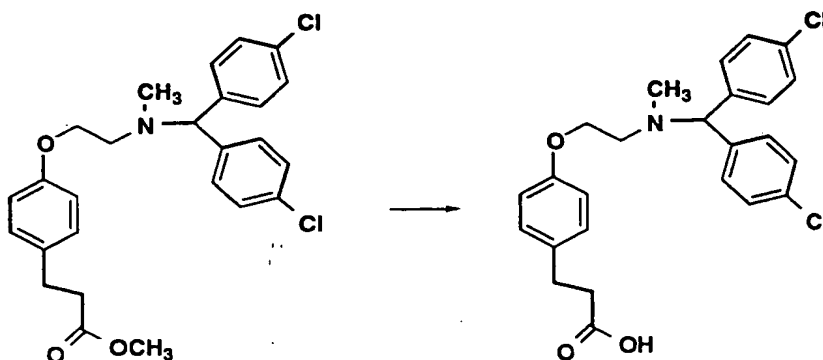
10

Anal. Calcd. for C₂₆H₂₇Cl₂NO₃ · 0.4 H₂O: C 65.11, H 5.84, N 2.92.

Found: C 65.34, H 5.89, N 3.08.

85

3-[4-[2-[N-[Bis-(4-chlorophenyl)methyl]methyl]-N-methylamino]ethoxy]phenyl]propanoic acid.



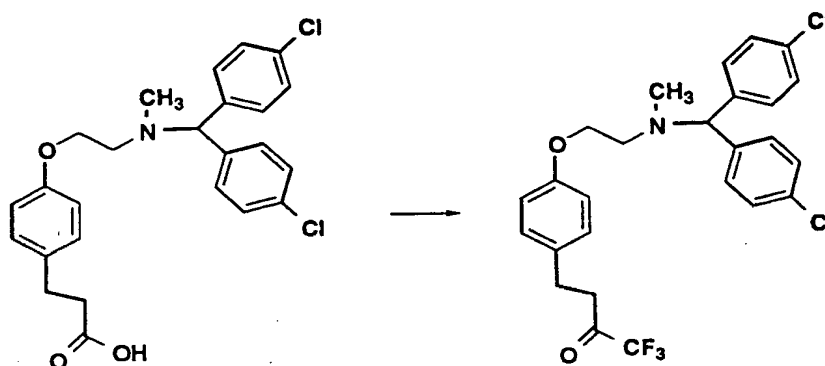
5

A solution of 3-[4-[2-(bis-(4-chlorophenyl)methyl]-N-methylamino]ethoxy]phenyl]-propanoic acid methyl ester (0.80 g, 1.7 mmol) in ethanol (7 ml) was treated with potassium hydroxide (0.2 g, 3.5 mmol) in water (2.4 ml) and the resulting mixture was stirred at 45°C for 2 h. The cooled mixture was adjusted to pH 4 with HCl 1N and concentrated *in vacuo*. The residue was partitioned between dichloromethane and water and the aqueous phase was extracted a second time with dichloromethane. The combined organic phases were dried over anhydrous magnesium sulfate and evaporated to give 0.746 g (95%) of the title material as an amorphous solid.

Anal. Calcd. for $C_{25}H_{25}Cl_2NO_3 \cdot 0.1 C_7H_8$: C 66.01, H 5.56, N 3.00.

Found: C 66.21, H 5.91, N 3.01.

4-[4-[2-[N-[Bis-(4-chlorophenyl)methyl]-N-methylamino]ethoxy]phenyl]-1,1,1-trifluoro-2-butanone.



5

A solution of 3-[4-[2-[N-[Bis-(4-chlorophenyl)methyl]-N-methylamino]ethoxy]phenyl]-propanoic acid (0.592 g, 1.29 mmol) in dichloromethane (10 ml) was treated at 22°C with oxalyl chloride (0.25 g, 1.97 mmol) and the resulting mixture was stirred for 1.5 h. The solvent was evaported *in vacuo* and the crude acid chloride was diluted with toluene (20 ml) and cooled to 0°C. Then trifluoroacetic anhydride (0.81 g, 3.87 mmol) was added followed by pyridine (0.22 g, 2.8 mmol) added dropwise over 10 min. The resulting mixture was then stirred at 22°C for 2.5 h. The mixture was then cooled to 0°C and treated dropwise with water (1 ml) and stirred for 15 min. The reaction mixture was then diluted with ethyl acetate, washed with saturated sodium bicarbonate, brine, and dried (magnesium sulfate). Evaporation of the solvent *in vacuo* and chromatography of the residue on silica gel (elution toluene ethyl acetate, 92:8) gave 0.465 g (70%) of title material as an oil.

Anal. Calcd. for C₂₆H₂₄Cl₂F₃NO₂: C 61.19, H 4.74, N 2.74.

Found: C 61.17, H 4.60, N 2.96.

20

The hydrochloride salt was obtained as an amorphous solid.

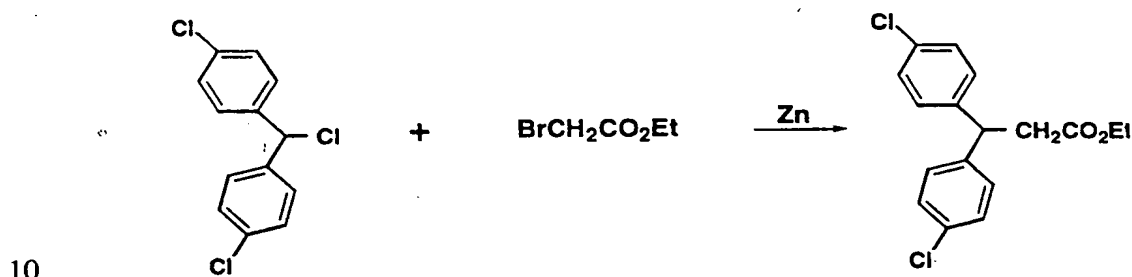
Anal. Calcd. for C₂₆H₂₄Cl₂F₃NO₂.HCl: C 57.11, H 4.61, N 2.56.

Found: C 57.09, H 4.97, N 2.38.

Example 10

5 4-[4-[2-[N-[3-Bis-(4-chlorophenyl)propyl]N-methylamino]ethoxy]phenyl]-1,1,1-trifluoro-2-butanone.

3-Bis-(4-chlorophenyl)propanoic acid, ethyl ester.

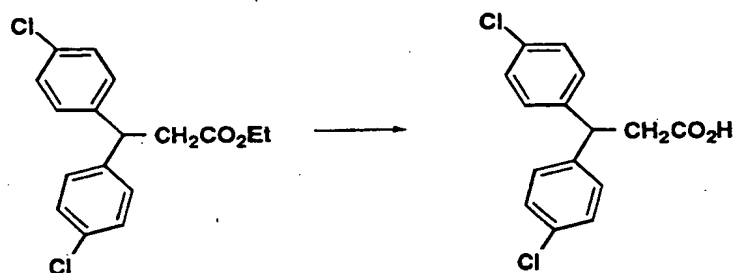


Ethyl bromoacetate (3.0 g, 18.0 mmol) was added dropwise to a boiling solution of zinc powder (1.7 g, 26.0 at g) and iodine (30.0 mg) in dichloromethane (5 ml) to form the Reformatsky reagent (K. Bott, 15 Tetrahedron Lett., 1984, 35, 555-556). The mixture was then cooled to 0°C and treated dropwise with a solution of 4,4'-dichlorobenzhydryl chloride (5.11 g, 15.8 mmol) in dichloromethane (10 ml) and the resulting mixture was stirred at 22°C for 3 h. The reaction mixture was then diluted with ether, washed with 10% sulfuric acid, brine and dried (magnesium sulfate). Evaporation of the solvent *in vacuo* gave an oil which was 20 chromatographed on silica gel to give 2.99 g (59%) of the title material as an oil: bp 110-115°C/0.1 torr.

Anal. Calcd. for C₁₇H₁₆Cl₂O₂: C 63.17, H 4.99.

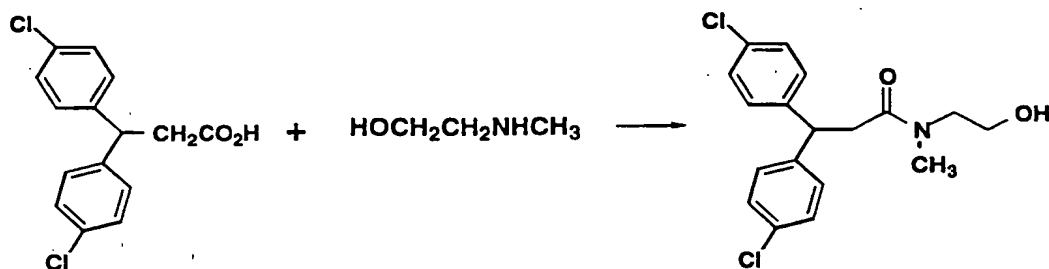
Found: C 62.94, H 4.90.

82

3-Bis-(4-chlorophenyl)propanoic acid.

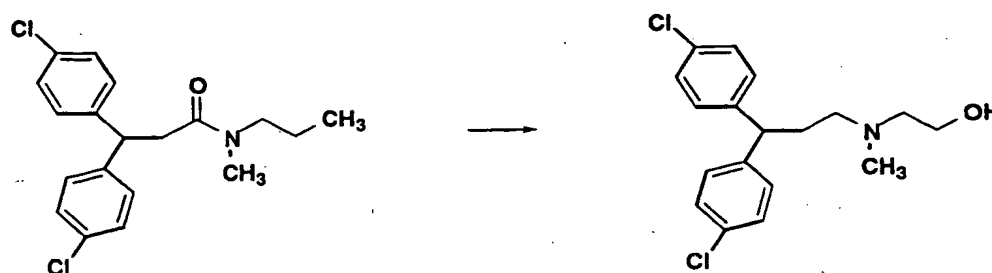
- 5 A solution of 3-Bis-(4-chlorophenyl)propanoic acid, ethyl ester (2.80 g, 8.66 mmol) in ethanol (40 ml) was treated with potassium hydroxide (1.0 g, 15.2 mmol) in water (10 ml) and the resulting mixture was heated at 60°C for 1 h. The cooled mixture was concentrated *in vacuo*, water and dichloromethane were added and the aqueous phase was adjusted to pH₃
- 10 with 2N hydrochloric acid. The aqueous phase was extracted two times with dichloromethane and the combined organic extracts were dried (magnesium sulfate). Evaporation of the solvent gave 2.40 g (94%) of the title material as a white solid: mp 188-189°C.

89

N-(2-Hydroxyethyl)-N-methyl-3-bis-(4-chlorophenyl)propanamide.

- 5 A solution of 3-Bis-(4-chlorophenyl)propanoic acid (2.33 g, 7.89 mmol) in dry dichloromethane (75 ml) was treated at 22°C with oxalyl chloride (2.18 g, 17.2 mmol) and a small drop of N,N-dimethyl formamide. After 1h, the solvent and excess reagent were evaporated *in vacuo*. The residual oil was diluted with dry tetrahydrofuran (10 ml) and added dropwise to a
- 10 vigorously stirred solution of 2-(methylamino) ethanol (0.75 g, 10.0 mmol) in tetrahydrofuran (15 ml) and water (15 ml) containing sodium bicarbonate (1 g). After 2 h at 22°C, the mixture was diluted with ethyl acetate, washed with brine and dried (magnesium sulfate). Evaporation of the solvent under vacuum and chromatography of the residue on silica
- 15 gel (elution dichloromethane-methanol 95:5) gave 2.63 g (93%) of the title material as an oil.

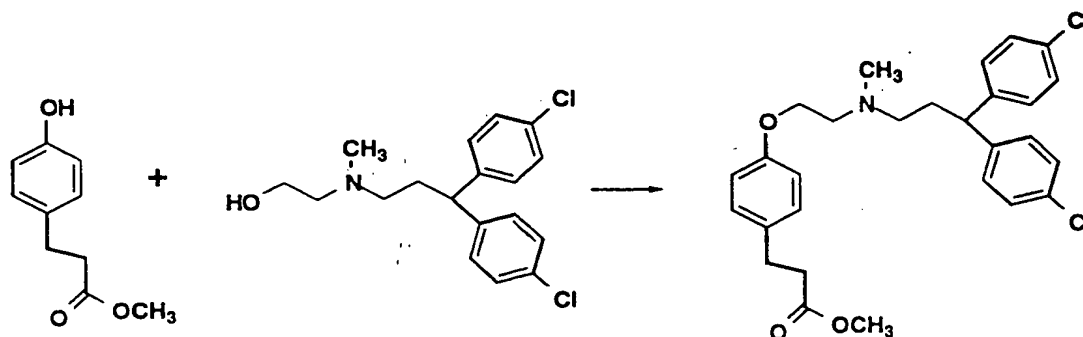
90

2-[N-[3-Bis-(4-chlorophenyl)propyl]-N-methylamino]ethanol.

- 5 A solution of N-(2-hydroxyethyl)-N-methyl-3-bis-(4-chlorophenyl)propanamide (2.63 g, 7.47 mmol) in dry tetrahydrofuran (35 ml) was treated with solid lithium aluminum hydride (0.66 g, 17.4 mmol) added in small portion over 10 min. The resulting mixture was then heated at 60°C for 2.5 h. The cooled solution was then quenched by
- 10 successive addition of water (1 ml), 10% sodium hydroxide (1 ml) and water (2 ml). The solid formed was filtered and the filtrate was dried (magnesium sulfate) and concentrated *in vacuo*. The residual oil was chromatographed on silica gel (elution ethyl acetate and methanol 0-20%) to give 1.72 g (68%) of the title material as an oil.
- 15 Anal. Calcd. for C₁₈H₂₁Cl₂NO: C 63.91, H 6.26, N 4.14.
Found: C 63.95, H 6.13, N 3.81.

91

3-[4-[2-[N-[3-Bis-(4-chlorophenyl)propyl]-N-methylamino]ethoxy]phenyl]-propanoic acid, methyl ester.



5

A solution of methyl 3-(4-hydroxyphenyl)propanoate (0.80 g, 4.44 mmol), 2-[N-[3-bis-(4-chlorophenyl)propyl]-N-methylamino]ethanol (1.62 g, 4.79 mmol) and triphenyl-phosphine (1.51 g, 5.76 mmol) in dry benzene (20 ml) was treated dropwise at 22°C with diethyl azodicarboxylate (1.00 g, 5.77 mmol). After 3h at 22°C, the reaction mixture was diluted in the ethyl acetate, washed with saturated sodium bicarbonate, brine and dried (magnesium sulfate).

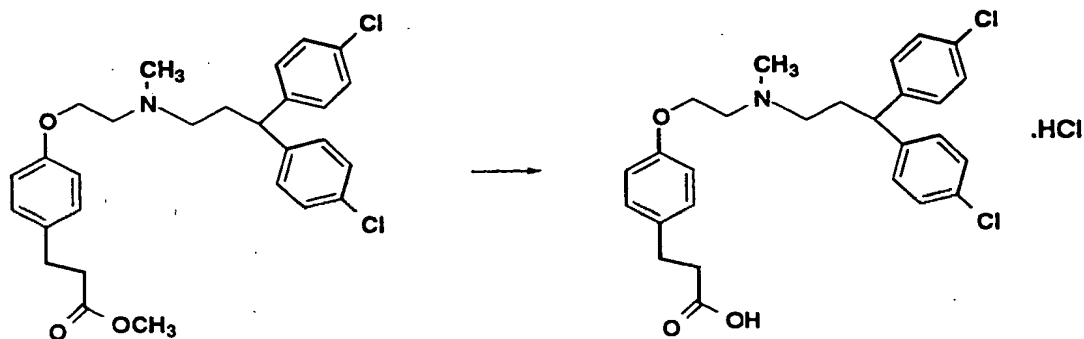
Evaporation of the solvent *under vacuo* and chromatography of the residue on silica gel (elution toluene-ethyl acetate 0-15%) gave 0.893 g (40%) of the title material as an oil.

Anal. Calcd. for $C_{28}H_{31}Cl_2NO_3 \cdot 0.2 H_2O$: C 66.72, H 6.28, N 2.78.

Found: C 66.60, H 6.31, N 2.92.

92

3-[4-[2-[N-[3-Bis-(4-chlorophenyl)propyl]-N-methylamino]ethoxy]phenyl]-propanoic acid, hydrochloride salt.



5

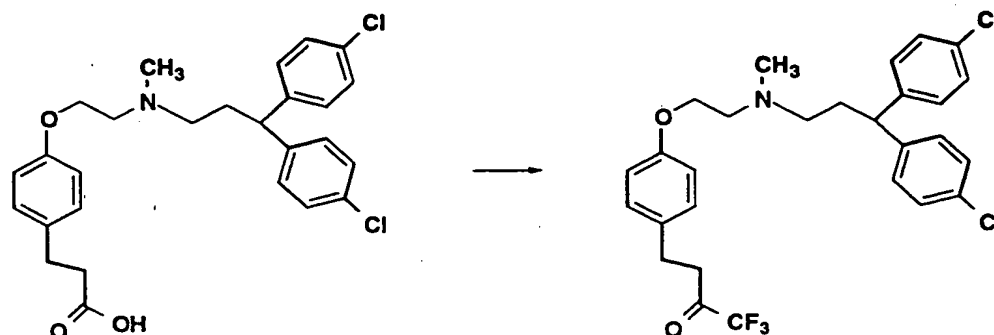
A solution of 3-[4-[2-[N-[3-Bis-(4-chlorophenyl)propyl]-N-methylamino]ethoxy]phenyl]-propanoic acid, methyl ester (0.801 g, 1.60 mmol) in ethanol (16 ml) was treated with potassium hydroxide (0.25 g, 3.8 mmol) in water (4 ml) and the resulting mixture was heated at 60°C for 1 h. After cooling, the reaction mixture was concentrated *in vacuo* and the residue was diluted with water and dichloromethane. The aqueous phase was adjusted to pH 4 with 2N hydrochloric acid and extracted two times with dichloromethane. The combined organic extracts were dried (magnesium sulfate) and evaporated *in vacuo* to give 0.700 g (90%) of the title material as a white foam.

Anal. Calcd. for $C_{27}H_{29}Cl_2NO_3 \cdot 0.7 HCl$: C 63.34, H 5.85, N 2.74.

Found: C 63.13, H 5.88, N 2.73.

93

4-[4-[2-[N-[3-Bis-(4-chlorophenyl)propyl]-N-methylamino]ethoxy]phenyl]-1,1,1-trifluoro-2-butanone.



5

A solution of 3-[4-[2-[N-[3-Bis-(4-chlorophenyl)propyl]-N-methylamino]ethoxy]phenyl] propanoic acid, hydrochloride salt (0.660 g, 1.36 mmol) in dry dichloromethane (30 ml) was treated with oxalyl chloride (0.45 g, 3.5 mmol) and a trace of N,N-dimethylformamide. After 1 h at 25°C, the solvent and excess reagents were evaporated *in vacuo*. The residual oil was dissolved in dry toluene (30 ml), cooled to 0°C and then treated with trifluoroacetic anhydride (0.6 ml, 4.25 mmol) followed by pyridine 0.3 ml, 3.71 mmol) added dropwise over 10 min. The resulting mixture was then stirred at 22°C for 2.5 h. After cooling again to 0°C, water (5 ml) was added dropwise and the mixture was stirred at 22°C for 30 min. The reaction mixture was then diluted with ethyl acetate, washed with saturated sodium bicarbonate, brine and dried (magnesium sulfate). Evaporation of the solvent under vacuum and chromatography of the residue on silica gel (elution gradient of toluene-ethyl acetate 1:1 to ethyl acetate) gave 0.307 g (42%) of the title material as an oil.

Anal. Calcd. for $C_{28}H_{28}Cl_2F_3NO_2 \cdot 0.5 H_2O$: C 61.43, H 5.34, N 2.56.

Found: C 61.46, H 5.13, N 2.60.

94

The hydrochloride salt was obtained as a white foam.

Anal. Calcd. for $C_{28}H_{28}Cl_2F_3NO_2 \cdot HCl \cdot H_2O$: C 56.72, H 5.27, N 2.36.

Found: C 56.95, H 4.97, N 2.23.

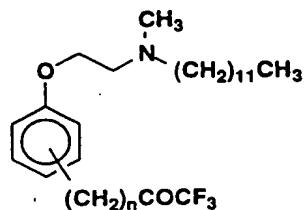
5

The following compounds may be prepared by the general procedure of Scheme 1.

95

SCHEME 1

TABLE A

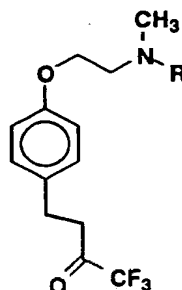


Example No.	Position	n	Analysis
11	meta	2	$\text{C}_{25}\text{H}_{40}\text{F}_3\text{NO}_2 \cdot \text{HCl} \cdot 1.3 \text{ H}_2\text{O}$ Calcd: C 59.64, H 8.73, N 2.78 Found: C 59.57, H 8.99, N 2.68
12	ortho	2	$\text{C}_{25}\text{H}_{40}\text{F}_3\text{NO}_2 \cdot \text{HCl} \cdot 0.4 \text{ H}_2\text{O}$ Calcd: C 61.32, H 8.65, N 2.87 Found: C 61.63, H 8.73, N 2.88
13	para	3	$\text{C}_{26}\text{H}_{42}\text{F}_3\text{NO}_2 \cdot \text{HCl} \cdot 0.7 \text{ H}_2\text{O}$ Calcd: C 61.53, H 8.83, N 2.76 Found: C 61.63, H 8.72, N 2.84
14	meta	1	$\text{C}_{24}\text{H}_{38}\text{F}_3\text{NO}_2 \cdot \text{HCl} \cdot 1.5 \text{ H}_2\text{O}$ Calcd: C 58.47, H 8.59, N 2.84 Found: C 58.43, H 8.29, N 3.12
15	para	3	$\text{C}_{26}\text{H}_{42}\text{F}_3\text{NO}_2 \cdot 0.4 \text{ H}_2\text{O}$ Calcd: C 67.18, H 9.28, N 3.01 Found: C 67.27, H 9.30, N 2.89
16	para	1	$\text{C}_{24}\text{H}_{38}\text{F}_3\text{NO}_2 \cdot \text{HCl} \cdot 0.4 \text{ H}_2\text{O}$ Calcd: C 60.91, H 8.48, N 2.96 Found: C 60.94, H 8.88, N 3.21

96

SCHEME 1

TABLE B




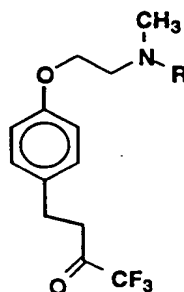
Example No.	R	Analysis
17	$(\text{CH}_2)_5\text{CH}_3$	$\text{C}_{19}\text{H}_{28}\text{F}_3\text{NO}_2 \cdot \text{HCl} \cdot 1.2 \text{ H}_2\text{O}$ Calcd: C 54.66, H 7.58, N 3.35 Found: C 54.64, H 7.42, N 3.47
18	$(\text{CH}_3)_7\text{CH}_3$	$\text{C}_{21}\text{H}_{32}\text{F}_3\text{NO}_2 \cdot \text{HCl} \cdot 0.7 \text{ H}_2\text{O}$ Calcd: C 57.78, H 7.94, N 3.21 Found: C 57.73, H 7.84, N 3.22
19	$(\text{CH}_2)_{17}\text{CH}_3$	$\text{C}_{31}\text{H}_{52}\text{F}_3\text{NO}_2 \cdot \text{HCl} \cdot 0.7 \text{ H}_2\text{O}$ Calcd: C 65.57, H 9.48, N 2.47 Found: C 65.58, H 9.85, N 2.78
20		$\text{C}_{28}\text{H}_{42}\text{F}_3\text{NO}_2 \cdot \text{HCl} \cdot 0.3 \text{ H}_2\text{O}$ Calcd: C 68.48, H 9.57, N 2.85 Found: C 68.51, H 9.36, N 2.86
21	$(\text{CH}_2)_3\text{C}_6\text{H}_5$	$\text{C}_{22}\text{H}_{26}\text{F}_3\text{NO}_2 \cdot 0.3 \text{ H}_2\text{O}$ Calcd: C 68.85, H 6.68, N 3.54 Found: C 66.73, H 6.51, N 3.61
22	$(\text{CH}_2)_3$  $\text{O}(\text{CH}_2)_3\text{CH}_3$	$\text{C}_{26}\text{H}_{34}\text{F}_3\text{NO}_3 \cdot \text{HCl} \cdot \text{H}_2\text{O}$ Calcd: C 60.05, H 7.17, N 2.69 Found: C 59.88, H 7.06, N 2.83

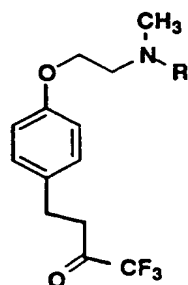
TABLE B (cont'd.)



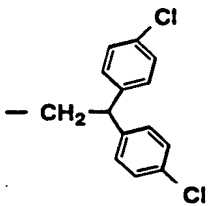
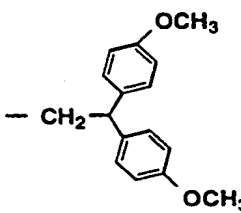
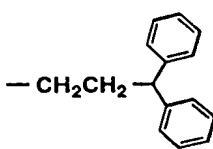
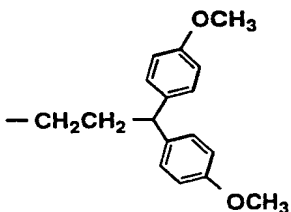
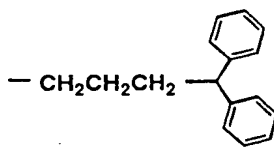
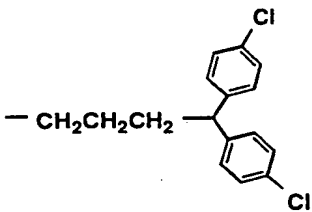
Example No.	R	Analysis
23		C ₂₆ H ₂₆ F ₃ NO ₂ . HCl.0.5 H ₂ O Calcd: C 64.13, H 5.80, N 2.88 Found: C 64.25, H 5.75, N 2.93
24		C ₂₆ H ₂₄ F ₅ NO ₂ . HCl.0.25 H ₂ O Calcd: C 60.24, H 4.96, N 2.70 Found: C 60.24, H 5.01, N 2.78
25		C ₂₈ H ₃₀ F ₃ NO ₄ . HCl.0.5 H ₂ O Calcd: C 61.48, H 5.90, N 2.56 Found: C 61.58, H 5.93, N 2.57
26		C ₂₈ H ₃₀ F ₃ NO ₄ . HCl.H ₂ O Calcd: C 60.48, H 5.98, N 2.52 Found: C 60.91, H 5.46, N 2.68

98

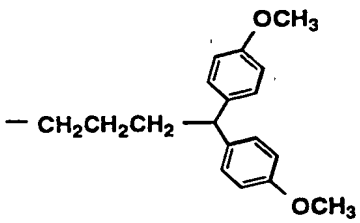
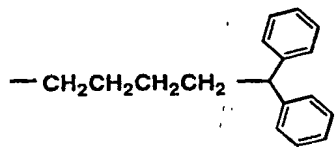
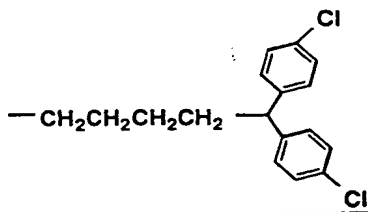
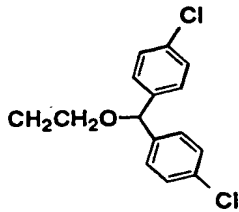
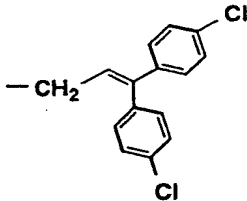
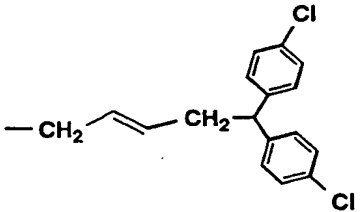
Scheme 1, Table B (continued)



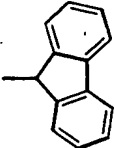
Exp. #	R	Analysis
27		$C_{27}H_{27}ClF_3NO_3 \cdot HCl \cdot 0.5 H_2O$ Calcd: C 58.81, H 5.30, N 2.54 Found: C 58.42, H 4.94, N 2.66
28		$C_{28}H_{28}Cl_2F_3NO_4 \cdot HCl \cdot 0.4 H_2O$ Calcd: C 54.76, H 4.89, N 2.28 Found: C 54.81, H 4.87, N 2.40
29		$C_{28}H_{29}ClF_3NO_4 \cdot HCl$ Calcd: C 58.75, H 5.28, N 2.45 Found: C 58.42, H 5.39, N 2.37
30		$C_{27}H_{26}Cl_2F_3NO_3 \cdot HCl \cdot 0.4 H_2O$ Calcd: C 55.52, H 4.80, N 2.40 Found: C 55.47, H 4.92, N 2.45
31		$C_{27}H_{28}F_3NO_2 \cdot 1.2 H_2O$ Calcd: C 63.13, H 6.16, N 2.73 Found: C 62.90, H 5.50, N 2.58

32		$C_{27}H_{26}Cl_2F_3NO_2 \cdot 0.5 H_2O$ Calcd: C 56.76, H 4.94, N 2.45 Found: C 56.40, H 4.99, N 2.48
33		$C_{29}H_{32}F_3NO_4 \cdot HCl \cdot H_2O$ Calcd: C 61.10, H 6.19, N 2.46 Found: C 61.17, H 5.88, N 2.27
34		$C_{28}H_{30}F_3NO_2 \cdot HCl \cdot H_2O$ Calcd: C 65.30, H 6.26, N 2.72 Found: C 65.30, H 6.36, N 3.10
35		$C_{30}H_{34}F_3NO_4 \cdot HCl \cdot 0.7 H_2O$ Calcd: C 62.27, H 6.34, N 2.42 Found: C 62.28, H 6.23, N 2.41
36		$C_{29}H_{32}F_3NO_2 \cdot HCl \cdot H_2O$ Calcd: C 64.74, H 6.56, N 2.60 Found: C 64.80, H 6.54, N 2.63
37		$C_{29}H_{30}Cl_2F_3NO_2 \cdot HCl \cdot H_2O$ Calcd: C 57.39, H 5.48, N 2.31 Found: C 57.07, H 5.45, N 2.30

160

38		$C_{31}H_{36}F_3NO_4 \cdot HCl \cdot H_2O$ Calcd: C 62.25, H 6.57 Found: C 61.89, H 6.37
39		$C_{30}H_{34}F_3NO_2 \cdot HCl \cdot 1.25 \cdot H_2O$ Calcd: C 64.74, H 6.79, N 2.52 Found: C 64.78, H 6.83, N 2.56
40		$C_{30}H_{32}Cl_2F_3NO_2 \cdot HCl \cdot 0.6 \cdot H_2O$ Calcd: C 58.71, H 5.62, N 2.28 Found: C 58.62, H 5.39, N 2.29
41		$C_{28}H_{28}Cl_2F_3NO_3 \cdot HCl \cdot 0.8 \cdot H_2O$ Calcd: C 55.56, H 5.10, N 2.31 Found: C 55.62, H 5.21, N 1.95
42		$C_{28}H_{26}Cl_2F_3NO_2 \cdot HCl \cdot H_2O$ Calcd: C 56.92, H 4.95, N 2.37 Found: C 56.51, H 4.63, N 2.35
43		$C_{30}H_{30}Cl_2F_3NO_2 \cdot HCl \cdot 1.5 H_2O$ Calcd: C 57.38, H 5.46, N 2.23 Found: C 57.57, H 5.36, N 2.23

101

44	 <chem>Cc1c2ccccc2c3ccccc13</chem>	C₂₆H₂₄F₃NO₂.HCl . 1.5 H₂O Calcd: C 62.09, H 5.61, N 2.78 Found: C 62.08, H 5.69, N 2.82
----	--	---

5

10

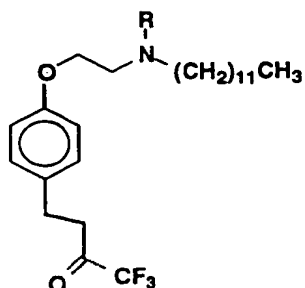
15

20

102

SCHEME 1

TABLE C

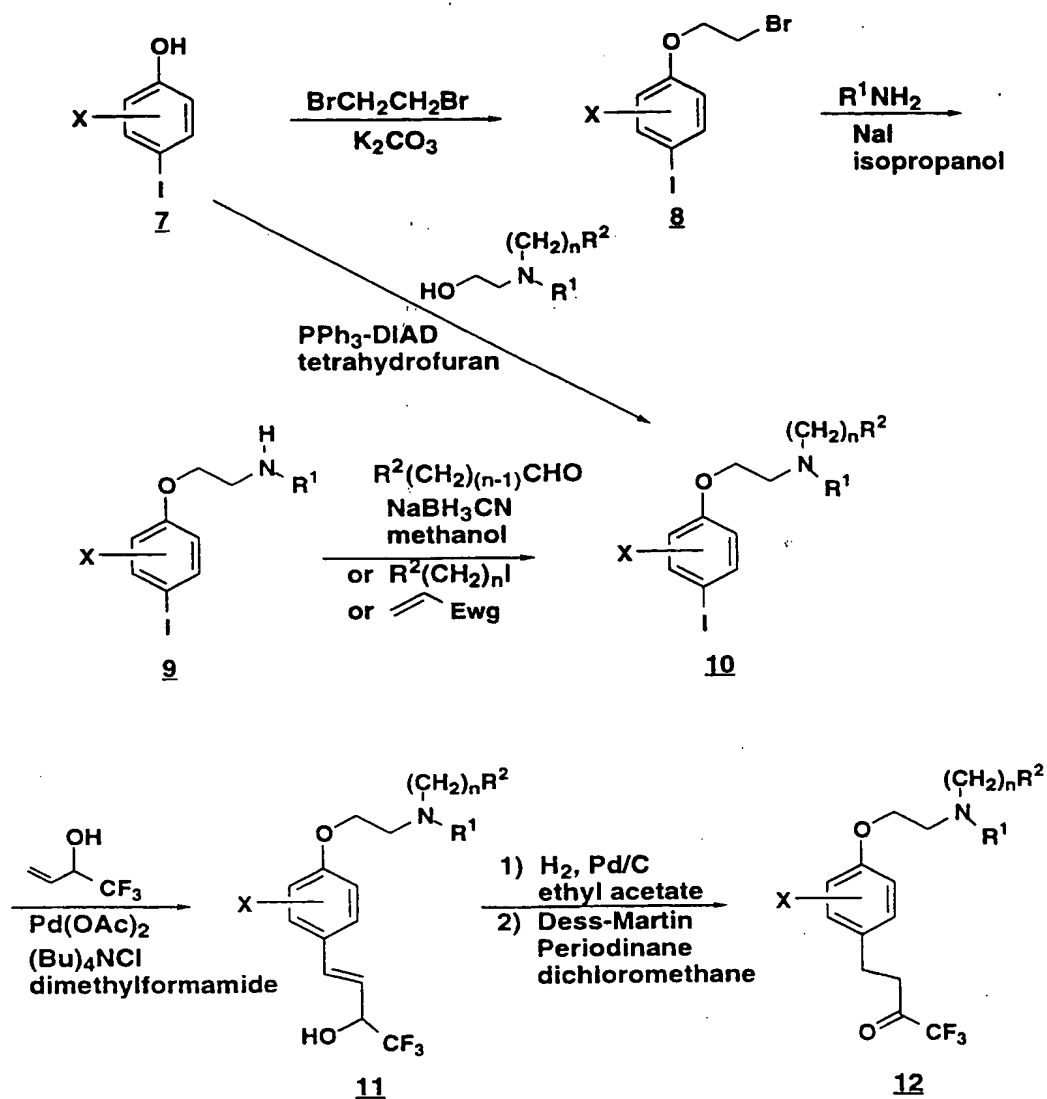


Example No.	R	Analysis
45	CH ₂ Ph	C ₃₁ H ₄₄ F ₃ NO ₂ . HCl. 1.2 H ₂ O Calcd: C 64.44, H 8.27, N 2.42 Found: C 64.53, H 8.27, N 2.37
46	(CH ₂) ₃ CH ₃	C ₂₈ H ₄₆ F ₃ NO ₂ . HCl. 1.5 H ₂ O Calcd: C 61.24, H 9.18, N 2.55 Found: C 61.34, H 9.14, N 2.60
47		C ₃₀ H ₄₆ F ₃ N ₃ O ₂ . HCl. H ₂ O Calcd: C 59.25, H 8.12, N 6.91 Found: C 59.51, H 7.59, N 6.90

5

10

103

Scheme 2

109

Example 48**4-[N-Dodecyl-N-[2-[4-(3-oxo-4,4,4-trifluorobut-1-yl)phenoxy]ethyl]amino]butanoic acid, ethyl ester**

5

Method I**1-[2-Bromoethoxy]-4-iodobenzene**

- 10 A mixture of 4-iodophenol (15.0g, 68.2mmol) and 1,2-dibromoethane (50ml, 580mmol) and potassium carbonate (14.0g, 0.1mol) was stirred and refluxed for 22h. After cooling to r.t., the mixture was filtered, washed with ethyl acetate and concentrated *in vacuo*. The residue was chromatographed on silica gel (Hexane/ethyl acetate 40 : 1 to 20 : 1) to
15 afford the title compound (18.7g, 84%) as a white solid.

N-2-[4-Iodophenoxy]ethyldodecylamine

- A mixture of dodecylamine (30g, 162mmol), diisopropylethylamine (22ml, 128mmol), sodium iodide (1.3g, 8.5mmol), 1-[2-bromoethoxy]-4-iodobenzene (13.9g, 42.5mmol) and isopropanol (250ml) was stirred and refluxed for 24h. After cooling to r.t., the mixture was filtered, washed with dichloromethane and concentrated *in vacuo*. The residue was chromatographed on silica gel (dichloromethane/methanol 50: 1 to 20 : 1)
20 to afford the title compound (15g, 82%) as a white solid.
Analysis for its hydriodide salt C₂₀H₃₄NIO·HI calcd. C 42.95%, H 6.31%, N 2.50%; Found: C 42.73%, H 6.16%, N 2.50%.

4-[N-dodecyl-N-2-[4-iodophenoxy]ethylamino]butanoic acid, ethyl ester

30

- To a mixture of N-2-[4-iodophenoxy]ethyldodecylamine (4.0g, 9.3mmol) and sodium cyanoborohydride (1.45g, 23mmol) in methanol (80ml) was added dropwise a solution of ethyl 4-oxobutyrate (Fournet, G. ; Balme, G.; Barieux, J.J. and Gore, J. *Tetrahedron*, 1988, 44, 5821) (2.4g, 18mmol) in
35 methanol (20ml) over a period of 10min. The resulting mixture was stirred at 22°C for 24h, and then diluted with ethyl acetate (600ml), washed with brine (3x250ml). The aqueous phase was extracted with ethyl

105

acetate (150ml), and the combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel (Hexane/ethyl acetate 8 : 1 to 6 : 1) to afford the title compound (4.5g, 89%) as a colorless oil.

- 5 Analysis for $C_{26}H_{44}NIO_3 \cdot 0.3H_2O$, calcd. C 56.68%, H 8.16%, N 2.54%;
Found: C 56.4% H 7.77%, N 2.63%.

4-[N-dodecyl-N-2-[4-(E)-[3-hydroxy-4,4,4-trifluorobut-1-en-1-yl]phenoxy]ethylamino]butanoic acid, ethyl ester

10

- To a solution of 4-[N-dodecyl-N-2-[4-iodophenoxy]ethylamino]butanoic acid, ethyl ester (4.5g, 8.3mmol) and 4,4,4-trifluorobut-1-en-3-ol (Pegolotti, J.A. and Young, W.G. *J. Amer. Chem. Soc.*, 1961, 83, 3251) (complex with 1 tetrahydrofuran, 3.3g, 16.6mmol) in N, N-dimethylformamide (17ml)
15 were added sodium bicarbonate (1.75g, 20.8mmol), tetrabutyl ammonium chloride hydrate (2.5g, 8.32mmol) and palladium (II) acetate (56mg, 0.25mmol). The resulting mixture was stirred at 50°C for 24h, and then diluted with ethyl acetate (300ml), washed with brine (100ml), sat. aq. sodium thiosulfate (2x100ml), brine (2x100ml),
20 dried over sodium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel (Hexane/ethyl acetate 4: 1 to 2 : 1) to afford the title compound (3.5g, 78%) as a colorless oil and 0.3g (6.6%) of 4-[N-Dodecyl-N-[2-[4-(4,4,4-trifluoro-3-oxo-but-1-yl)phenoxy]ethyl]amino]butanoic acid, ethyl ester.
25 Analysis for $C_{30}H_{48}F_3NO_4$ calcd. C 66.27%, H 8.90%, N 2.58%; Found: C 65.92%, H 8.73%, N 2.59%

4-[N-Dodecyl-N-2-[4-[3-hydroxy-4,4,4-trifluorobutyl]phenoxy]ethylamino]butanoic acid, ethyl ester

30

- A mixture of 4-[N-dodecyl-N-2-[4-(E)-[3-hydroxy-4,4,4-trifluorobut-1-en-1-yl]phenoxy]ethylamino] butanoic acid, ethyl ester (3.5g, 6.46mmol), palladium on activated carbon (10%, 0.6g) and ethyl acetate (250ml) was hydrogenated under 30psi for 6h. After filtration, the solvent was
35 removed *in vacuo* to give the title compound (3.3g, 94%) as a colorless oil.

4-[N-Dodecyl-N-[2-[4-(3-oxo-4,4,4-trifluorobut-1-yl)phenoxy]ethyl]amino]butanoic acid, ethyl ester

A suspension of 1,1, 1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one
5 (Dess-Martin periodinane, 1.7g, 4.0mmol) in dichloromethane (20ml) was
treated with 4-[N-dodecyl-N-2-[4-[4,4,4-trifluoro-3-
hydroxybutyl]phenoxy]ethylamino]butanoic acid, ethyl ester (430mg,
0.79mmol) dissolved in dichloromethane (5ml). The mixture was stirred
at 22°C for 4h, poured into a saturated aqueous sodium bicarbonate and
10 sodium thiosulfate (100ml) and extracted with ethyl acetate (2x100ml). The
combined organic layers were washed with sat. sodium bicarbonate
(2x60ml), brine (60ml), dried over sodium sulfate and concentrated *in vacuo*.
The residue was chromatographed on silica gel (hexane/ethyl
acetate 2 : 1 to 1.5 : 1) to afford the title compound (333mg, 77%) as a
15 colorless oil.

Analysis for $C_{30}H_{48}F_3N O_4 \cdot 1.1H_2O$ calcd. C 63.94%, H 8.98%, N 2.49%;
Found: C 63.55% H 8.55% N 2.61%.

Treatment of the above free amine with anhydrous hydrogen chloride (1.0
M in ether) gave the hydrochloride salt as a pale yellow syrup.

20

Example 49

3-[N-Dodecyl-N-[2-[4-(3-oxo-4,4,4-trifluorobut-1-yl)phenoxy]ethyl]amino]propanoic acid, ethyl ester

25

3-[N-Dodecyl-N-[2-[4-iodophenoxy]ethyl]amino]propanoic acid, ethyl ester

A mixture of N-2-[4-iodophenoxy]ethyldodecylamine (1.0g, 2.3mmol),
30 ethyl acrylate (1.2g, 12mmol) and ethanol (3ml) was stirred and refluxed
for 6h, and then concentrated *in vacuo*. The residue was
chromatographed on silica gel (hexane/ethyl acetate 8 : 1) to afford the
title compound (1.05g, 86%) as a colorless oil.

Analysis for $C_{25}H_{42}IN O_3$ calcd. C 56.49%, H 7.97%, N 2.64%; Found: C
35 56.79% H 8.10% N 2.59%.

107

3-[N-Dodecyl-N-2-[4-(E)-[3-hydroxy-4,4,4-trifluorobut-1-en-1-yl]phenoxy]ethylamino]propanoic acid, ethyl ester

5 [N-Dodecyl-N-2-[4-iodophenoxy]ethyl]amino]propanoic acid, ethyl ester (0.95g, 1.79mmol) and 4,4,4-trifluorobut-1-en-3-ol (complex with 0.7 THF, 0.95g, 5.4mmol) were reacted by the general procedure as described in the preparation of 4-[N-dodecyl-N-2-[4-(E)-[3-hydroxy-4,4,4-trifluorobut-1-en-1-yl]phenoxy]ethylamino]butanoic acid, ethyl ester (Example 48) and afforded the title compound (0.633g, 76%) as a colorless oil.

10

3-[N-Dodecyl-N-2-[4-[3-hydroxy-4,4,4-trifluorobutyl]phenoxy]ethylamino]propanoic acid, ethyl ester

15 [N-dodecyl-N-2-[4-(E)-[3-hydroxy-4,4,4-trifluorobut-1-en-1-yl]phenoxy]ethylamino]propanoic acid, ethyl ester (620mg, 1.17mmol) was hydrogenated as described in the preparation of 4-[N-dodecyl-N-2-[4-[3-hydroxy-4,4,4-trifluorobutyl]phenoxy]ethylamino]butanoic acid, ethyl ester (Example 48) and afforded the title compound (573mg, 92%) as a clear oil. Analysis for $C_{29}H_{48}F_3N O_4$ calcd. C 65.51%, H 9.10%, N 2.63%; Found: C 20 65.83% H 9.41% N 2.50%.

3-[N-Dodecyl-N-2-[4-(3-oxo-4,4,4-trifluorobut-1-yl)phenoxy]ethylamino]propanoic acid, ethyl ester

25 3-[N-Dodecyl-N-2-[4-[3-hydroxy-4,4,4-trifluorobutyl]phenoxy]ethylamino]propanoic acid, ethyl ester (320mg, 0.60mmol) was oxidized as described in the preparation of 4-[N-dodecyl-N-2-[4-(3-oxo-4,4,4-trifluorobut-1-yl)phenoxy]ethylamino]butanoic acid, ethyl ester (Example 48) and afforded the title compound (216mg, 68%) as a pale yellow oil.

30

Analysis for $C_{29}H_{46}F_3N O_4 \cdot 0.8H_2O$ calcd. C 64.02%, H 8.82%, N 2.57%; Found: C 63.94% H 8.85% N 2.59%.

Treatment of the above free amine with anhydrous hydrogen chloride (1.0 M in ether) gave the hydrochloride salt as a pale yellow syrup.

35

Analysis for $C_{29}H_{46}F_3N O_4 \cdot HCl \cdot 1.5H_2O$ calcd. C 58.72%, H 8.50%, N 2.36%; Found: C 58.45% H 8.22% N 2.55%.

Example 50

103

(2S, 4S)-1-N-Dodecyl-4-[4-(3-hydroxy-4,4,4-trifluorobut-1-yl)phenoxy]pyrrolidine-2-carboxylic acid, methyl ester

5 trans-4-Hydroxy-L-proline, methyl ester, hydrochloride

To a freshly prepared sat. solution of hydrogen chloride in methanol (100ml) was added *trans*-4-hydroxy-L-proline (10.0g, 76.26mmol). The resulting mixture was stirred at 22°C for 24h, concentrated *in vacuo* and
10 trituted with acetone at 0°C. Filtration afforded the title compound (12.8g, 92%) as a white solid.

(2S, 4R)-1-N-Dodecyl-4-hydroxypyrrolidine-2-carboxylic acid, methyl ester

15 A solution of *trans*-4-hydroxy-L-proline, methyl ester, hydrochloride (4.0g, 22.02mmol) and 1-iodododecane (3.04g, 44.04mmol) in methanol (30ml) was treated with potassium carbonate. The mixture was stirred and refluxed for 7h, cooled to r.t., diluted with ethyl acetate (700ml), washed with water (400ml), brine (200ml), dried over magnesium sulfate and
20 concentrated *in vacuo*. The residue was chromatographed on silica gel (petroleum ether/ethyl acetate 60 : 40 to 40 : 60) to afford the title compound (3.72g, 54%) as a white solid.

25 (2S, 4S)-1-N-Dodecyl-4-(4-iodophenoxy)pyrrolidine-2-carboxylic acid, methyl ester

(2S, 4R)-1-N-Dodecyl-4-hydroxypyrrolidine-2-carboxylic acid, methyl ester (1.75g, 7.94mmol) and 4-iodophenol (2.26g, 7.22mmol) were reacted under Mitsunobu conditions as described in the preparation of 3-[4-[2-(N-Dodecyl-N-methylamino)ethoxy]phenyl]propanoic acid, methyl ester. The
30 residue was chromatographed on silica gel (hexane/ethyl acetate 15 : 1 to 10 : 1) to afford the title compound (3.23g, 79%) as a white solid. $[\alpha]_D^{25} = -30.8^\circ$ (c 1.0, CHCl₃)
Analysis for C₂₄H₃₈INO₃ calcd. C 55.92%, H 7.43%, N 2.72%; Found: C 55.87%, H 7.48%, N 2.68%.
35

107

3-[N-Dodecyl-N-2-[4-(E)-[3-hydroxy-4,4,4-trifluorobut-1-en-1-yl]phenoxy]ethylamino]propanoic acid, ethyl ester

5 [N-Dodecyl-N-2-[4-iodophenoxy]ethyl]amino]propanoic acid, ethyl ester (0.95g, 1.79mmol) and 4,4,4-trifluorobut-1-en-3-ol (complex with 0.7 THF, 0.95g, 5.4mmol) were reacted by the general procedure as described in the preparation of 4-[N-dodecyl-N-2-[4-(E)-[3-hydroxy-4,4,4-trifluorobut-1-en-1-yl]phenoxy]ethylamino]butanoic acid, ethyl ester (Example 48) and afforded the title compound (0.633g, 76%) as a colorless oil.

10

3-[N-Dodecyl-N-2-[4-[3-hydroxy-4,4,4-trifluorobutyl]phenoxy]ethylamino]propanoic acid, ethyl ester

15 [N-dodecyl-N-2-[4-(E)-[3-hydroxy-4,4,4-trifluorobut-1-en-1-yl]phenoxy]ethylamino]propanoic acid, ethyl ester (620mg, 1.17mmol) was hydrogenated as described in the preparation of 4-[N-dodecyl-N-2-[4-[3-hydroxy-4,4,4-trifluorobutyl]phenoxy]ethylamino]butanoic acid, ethyl ester (Example 48) and afforded the title compound (573mg, 92%) as a clear oil. Analysis for C₂₉H₄₈F₃N O₄ calcd. C 65.51%, H 9.10%, N 2.63%; Found: C 65.83% H 9.41% N 2.50%.

20

3-[N-Dodecyl-N-2-[4-(3-oxo-4,4,4-trifluorobut-1-yl)phenoxy]ethyl]amino]propanoic acid, ethyl ester

25 3-[N-Dodecyl-N-2-[4-[3-hydroxy-4,4,4-trifluorobutyl]phenoxy]ethylamino]propanoic acid, ethyl ester (320mg, 0.60mmol) was oxidized as described in the preparation of 4-[N-dodecyl-N-2-[4-(3-oxo-4,4,4-trifluorobut-1-yl)phenoxy]ethyl]amino]butanoic acid, ethyl ester (Example 48) and afforded the title compound (216mg, 68%) as a pale yellow oil.

30

Analysis for C₂₉H₄₆F₃N O₄·0.8H₂O calcd. C 64.02%, H 8.82%, N 2.57%; Found: C 63.94% H 8.85% N 2.59%.

Treatment of the above free amine with anhydrous hydrogen chloride (1.0 M in ether) gave the hydrochloride salt as a pale yellow syrup.

35

Analysis for C₂₉H₄₆F₃N O₄·HCl·1.5H₂O calcd. C 58.72%, H 8.50%, N 2.36%; Found: C 58.45% H 8.22% N 2.55%.

Example 50

103

(2S, 4S)-1-N-Dodecyl-4-[4-(3-hydroxy-4,4,4-trifluorobut-1-yl)phenoxy]pyrrolidine-2-carboxylic acid, methyl ester

5 trans-4-Hydroxy-L-proline, methyl ester, hydrochloride

To a freshly prepared sat. solution of hydrogen chloride in methanol (100ml) was added *trans*-4-hydroxy-L-proline (10.0g, 76.26mmol). The resulting mixture was stirred at 22°C for 24h, concentrated *in vacuo* and
10 triturated with acetone at 0°C. Filtration afforded the title compound (12.8g, 92%) as a white solid.

(2S, 4R)-1-N-Dodecyl-4-hydroxypyrrolidine-2-carboxylic acid, methyl ester

15 A solution of *trans*-4-hydroxy-L-proline, methyl ester, hydrochloride (4.0g, 22.02mmol) and 1-iodododecane (3.04g, 44.04mmol) in methanol (30ml) was treated with potassium carbonate. The mixture was stirred and refluxed for 7h, cooled to r.t., diluted with ethyl acetate (700ml), washed with water (400ml), brine (200ml), dried over magnesium sulfate and
20 concentrated *in vacuo*. The residue was chromatographed on silica gel (petroleum ether/ethyl acetate 60 : 40 to 40 : 60) to afford the title compound (3.72g, 54%) as a white solid.

(2S, 4S)-1-N-Dodecyl-4-(4-iodophenoxy)pyrrolidine-2-carboxylic acid, methyl ester
25

(2S, 4R)-1-N-Dodecyl-4-hydroxypyrrolidine-2-carboxylic acid, methyl ester (1.75g, 7.94mmol) and 4-iodophenol (2.26g, 7.22mmol) were reacted under Mitsunobu conditions as described in the preparation of 3-[4-[2-(N-Dodecyl-N-methylamino)ethoxy]phenyl]propanoic acid, methyl ester. The
30 residue was chromatographed on silica gel (hexane/ethyl acetate 15 : 1 to 10 : 1) to afford the title compound (3.23g, 79%) as a white solid. $[\alpha]_D^{25} = -30.8^\circ$ (c 1.0, CHCl₃)

Analysis for C₂₄H₃₈INO₃ calcd. C 55.92%, H 7.43%, N 2.72%; Found: C
35 55.87%, H 7.48%, N 2.68%.

169

(2S, 4S)-1-N-Dodecyl-4-[4-(E)-[3-hydroxy-4,4,4-trifluorobut-1-en-1-yl]phenoxy]pyrrolidine-2-carboxylic acid, methyl ester

- 5 (2S, 4S)-1-N-Dodecyl-4-(4-iodophenoxy)pyrrolidine-2-carboxylic acid, methyl ester (800mg, 1.55mmol) and 4,4,4-trifluorobut-1-en-3-ol (complex with 1 tetrahydrofuran, 620mg, 3.1mmol) were reacted by the general procedure as described in the preparation of 4-[N-dodecyl-N-2-[4-(E)-[3-hydroxy-4,4,4-trifluorobut-1-en-1-yl]phenoxy]ethylamino]butanoic acid, ethyl ester and afforded the title compound (575mg, 72%) as a colorless oil
10 $[\alpha]_D = -28.7^\circ$ (c 0.8, CHCl_3) and (2S, 4S)-1-N-dodecyl-4-[4-(3-oxo-4,4,4-trifluorobut-1-yl)phenoxy]pyrrolidine-2-carboxylic acid, methyl ester (68mg, 9%) as a pale yellow oil.
Analysis for $\text{C}_{28}\text{H}_{42}\text{F}_3\text{N O}_4 \cdot 0.3\text{H}_2\text{O}$ calcd. C 64.79%, H 8.27%, N 2.70%; Found: C 64.74% H 8.23% N 2.87%.

15

(2S, 4S)-1-N-Dodecyl-4-[4-[3-hydroxy-4,4,4-trifluoro-1-buty]phenoxy]pyrrolidine-2-carboxylic acid, methyl ester

- (2S, 4S)-1-N-Dodecyl-4-[4-(E)-[3-hydroxy-4,4,4-trifluorobut-1-en-1-yl]phenoxy]pyrrolidine-2-carboxylic acid, methyl ester (552mg., 1.07mmol)
20 was hydrogenated as described in the preparation of 4-[N-dodecyl-N-2-[4-[3-hydroxy-4,4,4-trifluorobutyl]phenoxy]ethylamino]-butanoic acid, ethyl ester and afforded the title compound (546mg, 99%) as a clear oil. $[\alpha]_D = -89.0^\circ$ (c 0.4, CHCl_3)
25 Analysis for $\text{C}_{28}\text{H}_{44}\text{F}_3\text{N O}_4$ calcd. C 65.22%, H 8.60%, N 2.72%; Found: C 65.13% H 8.59% N 2.68%.

Example 51

- 30 (2S, 4S)-1-N-Dodecyl-4-[4-(3-oxo-4,4,4-trifluorobut-1-yl)phenoxy]pyrrolidine-2-carboxylic acid, methyl ester

(2S, 4S)-1-N-Dodecyl-4-[4-[3-hydroxy-4,4,4-trifluorobutyl]phenoxy]pyrrolidine-2-carboxylic acid, methyl ester (425mg,
35 0.825mmol) was oxidized as described in the preparation of 4-[N-dodecyl-N-2-[4-(3-oxo-4,4,4-trifluorobut-1-yl)phenoxy]ethylamino]butanoic acid,

ethyl ester and afforded the title compound (272mg, 64%) as a pale yellow oil.

Analysis for $C_{28}H_{42}F_3N O_4 \cdot 0.4H_2O$ calcd. C 64.57%, H 8.28%, N 2.69%;

Found: C 64.61% H 8.08% N 2.76%.

- 5 Treatment of the above free amine with anhydrous hydrogen chloride (1.0 M in ether) gave the hydrochloride salt as a pale yellow foam. $[a]_D = -9.2^\circ$ (c 0.74, $CHCl_3$)

$C_{28}H_{43}F_3N O_4 \cdot HCl \cdot 1.2H_2O$ calcd. C 58.82%, H 8.00%, N 2.45%; Found: C 58.79% H 7.85% N 2.41%.

10

Example 52

(2S, 4S)-1-Dodecyl-4-[4-(3-oxo-4,4,4-trifluorobut-1-yl)phenoxy]pyrrolidine-2-propanoic acid, methyl ester

15

(2S, 4S)-1-N-Dodecyl-4-(4-iodophenoxy)pyrrolidine-2-methanol

- To a solution of (2S, 4S)-1-N-dodecyl-4-(4-iodophenoxy)pyrrolidine-2-carboxylic acid, methyl ester (2.09g, 4.06mmol) in tetrahydrofuran (20ml) at -78°C was added dropwise diisobutylaluminum hydride (1.0M in hexane, 15.0ml, 15.0mmol). After stirring at this temperature for 5min. and at 0°C for 2.5h, the reaction was quenched with water at 0°C. After stirring at r.t. for 10min., the mixture was diluted with ethyl acetate (250ml), washed with 2N sodium hydroxide (3x100ml), 35% sodium and potassium tartrate (2x100ml), brine (100ml), dried over sodium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane/ethyl acetate 3 : 1 to 2 : 1) to afford the title compound (1.65g, 79%) as a colorless oil. $[a]_D = -18.5^\circ$ (c 0.92, $CHCl_3$).

- 25 Analysis for $C_{23}H_{38}F_3INO_2$ calcd. C 56.67%, H 7.86%, N 2.87%; Found: C 56.65% H 7.39% N 2.95%.

30

(2S, 4S)-1-N-Dodecyl-4-(4-iodophenoxy)pyrrolidine-2-propenoic acid, methyl ester

- 35 To a solution of oxalyl chloride (1.1ml, 12.1mmol) in dichloromethane (17ml) at -60°C was added dropwise dimethylsulfoxide (1.7ml, 24.2mmol). After stirring for 5min., a solution of (2S, 4S)-1-N-dodecyl-4-(4-

111

iodophenoxy)- pyrrolidine-2-methanol (1.18g, 2.42mmol) in dichloromethane (6ml) was then added dropwise. The resulting mixture was stirred, and the temperature allowed to rise gradually to -20°C over a period of 2h. The reaction was quenched with sat. ammonium chloride, 5 diluted with dichloromethane, washed three times with sat. ammonium chloride, brine and dried over sodium sulfate. The solvent was removed *in vacuo* to afford the corresponding aldehyde which was directly used in the next step.

10 The above material was dissolved in dichloromethane (20ml) and treated with methyl (triphenyl-phosphoranylidene) acetate (1.44g, 4.3mmol). The mixture was stirred at 22°C for 22h and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane/ethyl acetate 15 : 1 to 10 : 1) to afford E-- (2 S, 4S)-1-N-Dodecyl-4-(4-iodophenoxy)pyrrolidine-2-
15 propenoic acid, methyl ester (934mg, 61%) as a white solid [m.p. 60-61°C, $[\alpha]_D = -42.2^\circ$ (c 0.96, CDCl_3)] and Z- (2 S, 4S)-1-N-dodecyl-4-(4-iodophenoxy)pyrrolidine-2-propenoic acid, methyl ester (149mg, 9%) as a clear oil. $[\alpha]_D = -79.3^\circ$ (c 1.24, CHCl_3).
Analysis for E-isomer $\text{C}_{26}\text{H}_{40}\text{INO}_3$ calcd. C 57.67%, H 7.45%, N 2.59%;
20 Found: C 57.41% H 7.50% N 2.64%.

(2S, 4S)-1-N-Dodecyl-4-[4-(E)-[3-hydroxy-4,4,4-trifluorobut-1-en-1-yl]phenoxy]pyrrolidine-2-propenoic acid, methyl ester

25 (2S, 4S)-1-N-Dodecyl-4-(4-iodophenoxy)pyrrolidine-2-propenoic acid, methyl ester (677mg, 1.24mmol) and 4,4,4-trifluorobut-1-en-3-ol (complex with 1 tetrahydrofuran, 1.23g, 6.2mmol) were reacted by the general procedure as described in the preparation of 4-[N-dodecyl-N-2-[4-(E)-[3-hydroxy-4,4,4-trifluorobut-1-en-1-yl]phenoxy]ethylamino]butanoic acid,
30 ethyl ester and afforded the title compound (250mg, 37%) as a colorless oil.
Analysis for $\text{C}_{30}\text{H}_{44}\text{F}_3\text{N O}_4 \cdot 0.2\text{H}_2\text{O}$ calcd. C 66.32%, H 8.24%, N 2.58%;
Found: C 66.14% H 8.03% N 2.55%.

(2S, 4S)-1-N-Dodecyl-4-[4-[3-hydroxy-4,4,4-trifluoro-1-butyl]phenoxy]pyrrolidine-2-propanoic acid, methyl ester

- 5 (2S, 4S)-1-N-Dodecyl-4-[4-(E)-[3-hydroxy-4,4,4-trifluorobut-1-en-1-yl]phenoxy]pyrrolidine-2-propanoic acid, methyl ester (260mg, 0.482mmol) was hydrogenated as described in the preparation of 4-[N-dodecyl-N-2-[4-[3-hydroxy-4,4,4-trifluorobutyl]phenoxy] ethylamino]-butanoic acid, ethyl ester and afforded the title compound (185mg, 71%) as a colorless oil. $[\alpha]_D = -35.3^\circ$ (c 0.85, CHCl_3)
- 10 Analysis for $\text{C}_{30}\text{H}_{48}\text{F}_3\text{N O}_4 \cdot 0.1\text{H}_2\text{O}$ calcd. C 66.05%, H 8.91%, N 2.57%; Found: C 65.89% H 8.68% N 2.51%.

(2S, 4S)-1-N-Dodecyl-4-[4-(3-oxo-4,4,4-trifluorobut-1-yl)phenoxy]pyrrolidine-2-propanoic acid, methyl ester

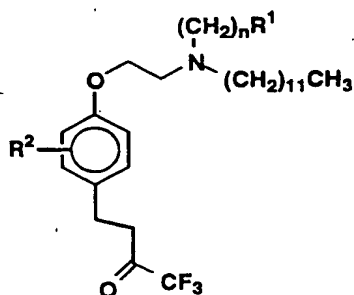
- 15 (2S, 4S)-1-N-Dodecyl-4-[4-[3-hydroxy-4,4,4-trifluorobutyl]phenoxy]pyrrolidine-2-propanoic acid, methyl ester (150mg, 0.276mmol) was oxidized as described in the preparation of 4-[N-dodecyl-N-[2-[4-(3-oxo-4,4,4-trifluorobut-1-yl)phenoxy]ethyl]amino]butanoic acid,
- 20 ethyl ester and afforded the title compound (70mg, 47%) as a pale yellow oil. $[\alpha]_D = -35.7^\circ$ (c 0.84, CDCl_3)
- Treatment of the above free amine with anhydrous hydrogen chloride (1.0 M in ether) gave the hydrochloride salt as a pale yellow foam.
- $\text{C}_{30}\text{H}_{46}\text{F}_3\text{N O}_4 \cdot \text{HCl} \cdot 1.1\text{H}_2\text{O}$ calcd. C 60.26%, H 8.29%, N 2.34%; Found: C
- 25 60.29% H 8.10% N 2.34%.

The following compounds may be prepared by the general procedure of Scheme 2.

113

SCHEME 2

TABLE A

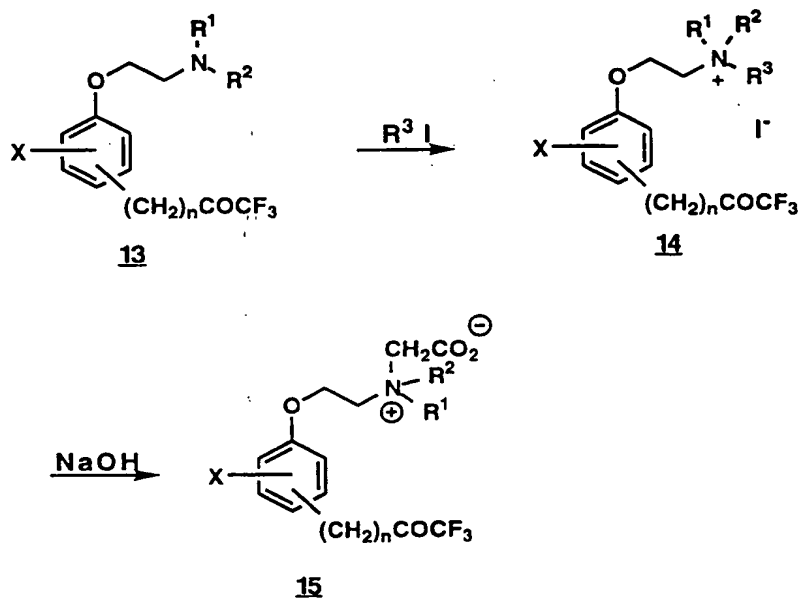


Exp. #	n	R ¹	R ²	Analysis
53	1	CO ₂ Et	H	C ₂₈ H ₄₄ F ₃ NO ₄ . HCl.1.5 H ₂ O Calcd: C 58.07, H 8.35, N 2.42 Found: C 57.95, H 8.29, N 2.45
54	4	CO ₂ Et	H	C ₃₁ H ₅₀ F ₃ NO ₄ . HCl.1.5 H ₂ O Calcd: C 59.94, H 8.76, N 2.25 Found: C 59.80, H 8.46, N 2.17
55	3	CO ₂ H	H	C ₂₈ H ₄₄ F ₃ NO ₄ . 0.7 HCl Calcd: C 62.14, H 8.33, N 2.59 Found: C 62.25, H 8.36, N 2.58
56	4	CO ₂ H	H	C ₂₉ H ₄₆ F ₃ NO ₄ . HCl Calcd: C 61.52, H 8.37, N 2.47 Found: C 61.91, H 8.28, N 2.51
57	4		H	C ₃₃ H ₅₄ F ₃ NO ₄ . HCl .0.7 H ₂ O Calcd: C 62.43, H 8.95, N 2.21 Found: C 62.48, H 9.10, N 2.14
58	1	H	2-F	C ₂₅ H ₃₉ F ₄ NO ₂ . HCl .1.6 H ₂ O Calcd: C 56.99, H 8.26, N 2.66 Found: C 57.00, H 8.14, N 2.65

119

59	1	H	3-CH ₂ Ph	$C_{32}H_{46}F_3NO_2 \cdot HCl \cdot 0.7 H_2O$ Calcd: C 65.95, H 8.37, N 2.40 Found: C 65.93, H 8.41, N 2.20
----	---	---	----------------------	--

115

Scheme 3

Example 60**N,N-Dimethyl-N-[2-[4-(3-oxo-4,4,4-trifluorobut-1-yl)-phenoxy]ethyl] dodecyl- ammonium, iodide**

5

A solution of 4-[4-[2-(N-Dodecyl-N-methylamino)ethoxy]phenyl]-1,1,1-trifluoro-2-butanone (250mg, 0.56mmol) in isopropanol (6ml) and methyl iodide (2ml) was heated to reflux for 0.5h. After cooling to r.t., the mixture was evaporated *in vacuo* and the last traces of isopropanol co-evaporated with dichloromethane to afford the title compound (327mg, 100%) as a yellow waxy solid.

10

Analysis for $C_{26}H_{43}F_3INO_2 \cdot 0.7H_2O$ calcd. C 52.21%, H 7.48%, N 2.34%; Found: C 52.21%, H 7.43%, N 2.40%.

15

Example 61**N,N-Dimethyl-N-[2-[3-(3-oxo-4,4,4-trifluorobut-1-yl)-phenoxy]ethyl] dodecyl- ammonium, iodide**

20

4-[3-[2-(N-Dodecyl-N-methylamino)ethoxy]phenyl]-1,1,1-trifluoro-2-butanone (300mg, 0.68mmol) was reacted by the general procedure as described in the preparation of N,N-dimethyl-N-[2-[4-(3-oxo-4,4,4-trifluorobut-1-yl)-phenoxy]ethyl] dodecyl- ammonium, iodide and afforded the title compound (397mg, 100%) as a yellow syrup.

25

Analysis for $C_{26}H_{43}F_3INO_2 \cdot 1H_2O$ calcd. C 51.74%, H 7.52%, N 2.32%; Found: C 51.90%, H 7.58%, N 2.32%.

Example 62

30

N,N-Dimethyl-N-[2-[2-(3-oxo-4,4,4-trifluorobut-1-yl)-phenoxy]ethyl] dodecyl- ammonium, iodide

4-[2-[2-(N-Dodecyl-N-methylamino)ethoxy]phenyl]-1,1,1-trifluoro-2-butanone (417mg, 0.94mmol) was reacted by the general procedure as described in the preparation of N,N-dimethyl-N-[2-[4-(3-oxo-4,4,4-trifluorobut-1-yl)-phenoxy]ethyl] dodecyl- ammonium, iodide and afforded the title compound (550mg, 100%) as a yellow syrup.

35

117

Analysis for $C_{26}H_{43}F_3INO_2 \cdot 0.5H_2O$ calcd. C 52.53%, H 7.46%, N 2.36%;
Found: C 52.46%, H 7.42%, N 2.42%.

Example 63

5

N,N-Dimethyl-N-[2-[2-(trifluoroacetyl)phenoxy]ethyl] dodecylammonium, iodide

[2-[2-(N,N-Dimethylamino)ethoxy]phenyl]-2,2,2-trifluoroethanone

10

A mixture of 2-trifluoroacetylphenol (380mg, 2.0mmol), 2-[N, N-dimethylamino]ethyl chloride, hydrochloride (432mg, 6.0mmol) potassium carbonate (1.38g, 10mmol) and toluene (5ml) was refluxed for 3.5h. After cooling to r.t., the mixture was treated with water and ether.

15 The organic layer was washed twice with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel (acetone/ether 1 : 1 to 1 : 0) to give the title compound (375mg, 72%) as a white solid.

20 N,N-Dimethyl-N-[2-[2-(trifluoroacetyl)phenoxy]ethyl] dodecylammonium, iodide

A mixture of [2-[2-(N,N-Dimethylamino)ethoxy]phenyl]-2,2,2-trifluoroethanone (416mg, 1.59mmol), 1-iodododecane (1.42g, 4.8mmol)
25 and isopropanol (20ml) was refluxed for 24h. After cooling to r.t., the solvent was removed *in vacuo*. The residue was chromatographed on silica gel [dichloromethane/methanol/ammonium hydroxide (28%) 90 : 10 : 1 to 85 : 15 : 1] to give a pale yellow solid. Recrystallization from acetone/ether (1 : 3) afforded the title compound (512mg, 58%) as fine
30 needles.

Analysis for $C_{24}H_{39}F_3INO_2$ calcd. C 51.71%, H 7.05%, N 2.51%; Found: C 51.83%, H 7.07%, N 2.51%.

35

Example 64**N,N-Dimethyl-N-[2-[2-(trifluoroacetyl)phenoxy]ethyl]octadecylammonium, iodide**

5

[2-[2-(N,N-Dimethylamino)ethoxy]phenyl]-2,2,2-trifluoroethanone (400mg, 1.5mmol) and 1-iodooctadecane (1.8g, 4.8mmol) were reacted by the general procedure as described in the preparation of N,N-dimethyl-N-[2-[2-(trifluoroacetyl)phenoxy]ethyl] dodecylammonium, iodide.

10 Recrystallization from Acetone/ether (1 : 2) afforded the title compound (500mg, 52%) as fine needles.

Analysis for C₃₀H₅₁F₃INO₂ calcd. C 56.16%, H 8.01%, N 2.18%; Found: C 56.06%, H 7.90%, N 2.13%.

15 **Example 65****N,N-Dimethyl-N-[2-[4-(trifluoroacetyl)phenoxy]ethyl]octadecylammonium, iodide**20 **N,N-Dimethyl-2-(4-bromophenoxy)ethylamine**

A mixture of 4-bromophenol (5.0g, 28.9mmol), 2-(N, N-dimethylamino)ethyl chloride, hydrochloride (6.24g, 43.4mmol), sodium iodide (600mg, 4mmol), cesium carbonate (28g, 86.7mmol) and methyl
25 ethyl ketone (120ml) was heated to reflux for 4h. After cooling to r.t., the mixture was filtered and washed with acetone. The combined filtrates were concentrated *in vacuo*, and the residue was chromatographed on silica gel (dichloromethane/methanol 95 : 5 to 90 : 10) to give a pale yellow
liquid. Bulb-to-bulb distillation (80-84°C/0.05mmHg) afforded the title
30 compound (5.19g, 74%) as a colorless liquid.

[4-[2-(N,N-Dimethylamino)ethoxy]phenyl]-2,2,2-trifluoroethanone

To a solution of N,N-dimethyl-2-(4-bromophenoxy)ethylamine (1.0g, 4.1mmol) in tetrahydrofuran (10ml) at -78°C was added dropwise n-butyllithium (1.5M in hexane, 2.7ml, 4.1mmol). The mixture was stirred at this temperature for 15min. and then transferred via a cannula into a
35

119

pre-cooled solution of ethyl trifluoroacetate (0.64g, 4.5mmol) in ether (8ml) at -78°C. The resulting mixture was stirred and the temperature allowed to rise gradually to r.t. over a period of 1.5h. The reaction mixture was then quenched with water (5ml) and diluted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. Bulb-to-bulb distillation (82-84°C/0.01mmHg) afforded the title compound (423mg, 39%) as a pale yellow oil. Analysis for C₁₂H₁₄F₃NO₂ · 0.3H₂O calcd. C 54.05%, H 5.52%, N 5.25%; Found: C 54.12%, H 5.39%, N 5.28%.

10

N,N-Dimethyl-N-[2-[4-(trifluoroacetyl)phenoxy]ethyl] octadecylammonium, iodide

15

[4-[2-(N,N-Dimethylamino)ethoxy]phenyl]-2,2,2-trifluoroethanone (343mg, 1.31mmol) and 1-iodooctadecane (1.16g, 53.93mmol) were reacted by the general procedures as described in the preparation of N,N-dimethyl-N-[2-[2-(trifluoroacetyl)phenoxy]ethyl] dodecylammonium, iodide. The residue was chromatographed on silica gel [dichloromethane/methanol/ammonium hydroxide (28%) 98 : 2 : 0.5 to 90 : 10 : 1] to give the title compound (722mg, 86%) as a white solid. Analysis for C₃₀H₅₁F₃INO₂ calcd. C 56.16%, H 8.01%, N 2.18%; Found: C 56.33%, H 7.79%, N 2.09%.

20

Example 66

25

N,N-Dimethyl-N-[2-[3-(trifluoroacetyl)phenoxy]ethyl] octadecylammonium, iodide

N,N-Dimethyl-2-(3-bromophenoxy)ethylamine

30

3-Bromophenol (5.0g, 28.9mmol) and 2-(N, N-dimethylamino)ethyl chloride, hydrochloride (6.24g, 43.3mmol) were reacted by the general procedures as described in the preparation of N,N-dimethyl-2-(4-bromophenoxy)ethylamine. The residue was chromatographed on silica gel (dichloromethane/methanol 100 : 0 to 90 : 10) to give the title compound (5.2g, 74%) as a pale yellow liquid.

35

[3-[2-(N,N-Dimethylamino)ethoxy]phenyl]-2,2,2-trifluoroethanone

N,N-Dimethyl-2-(3-bromophenoxy)ethylamine (2.87g, 11.7mmol) and ethyl trifluoroacetate (2.5g, 17.6mmol) were reacted by the general
5 procedure as described in the preparation of [4-[2-(N,N-dimethylamino)ethoxy]phenyl]-2,2,2-trifluoroethanone. The residue was distilled under reduced pressure to afford the title compound (1.34g, 44%) as a pale yellow liquid. Analytically pure sample was obtained by a second distillation under reduced pressure. Analysis for $C_{12}H_{14}F_3NO_2 \cdot 0.8H_2O$
10 calcd. C 52.29%, H 5.70%, N 5.08%; Found: C 52.61%, H 5.53%, N 4.96%.

N,N-Dimethyl-N-[2-[3-(Trifluoroacetyl)phenoxy]ethyl]octadecylammonium, iodide

15 [3-[2-(N,N-Dimethylamino)ethoxy]phenyl]-2,2,2-trifluoroethanone (438mg, 1.67mmol) and 1-iodooctadecane (1.9g, 5.0mmol) were reacted by the general procedure as described in the preparation of N,N-dimethyl-N-[2-[2-(trifluoroacetyl)phenoxy]ethyl] dodecylammonium, iodide. Recrystallization from acetone/ether (1 : 2) afforded the title compound
20 (530mg, 50%) as fine needles. Analysis for $C_{30}H_{51}F_3INO_2 \cdot 0.2H_2O$ calcd. C 55.84%, H 8.03%, N 2.17%; Found: C 55.79%, H 7.98%, N 2.10%.

Example 67

25

N-[(Ethoxycarbonyl)methyl]-N-[2-[4-(3-oxo-4,4,4-trifluorobut-1-yl)phenoxy]ethyl]-N-(methyl)- dodecylammonium, iodide

A solution of 4-[4-[2-(N-Dodecyl-N-methylamino)ethoxy]phenyl]-1,1,1-trifluoro-2-butanone (620mg, 1.4mmol) and ethyl iodoacetate (0.5ml, 4.2mmol) in ethanol (20ml) was heated to reflux for 3h. After cooling to r.t., the mixture was concentrated *in vacuo*. The residue was chromatographed on silica gel [dichloromethane/methanol/ ammonium hydroxide (28%) 95 : 5 : 0.5 to 90 : 10 : 1] to give a colorless syrup. This
30 material was dissolved in aqueous tetrahydrofuran (90%), evaporated *in vacuo* and co-evaporated with acetonitrile to afford the title compound (855mg, 93%) as a colorless syrup.
35

12]

Example 68**N-(Carboxymethyl)-N-[2-[4-(3-oxo-4,4,4-trifluorobut-1-yl)phenoxy]ethyl]-N-(methyl)dodecyl ammonium, hydroxide, inner salt**

5

A solution of N-[(ethoxycarbonyl)methyl]-N-[2-[4-(3-oxo-4,4,4-trifluorobut-1-yl)phenoxy]ethyl]-N-(methyl)- dodecylammonium, iodide (617mg, 0.938mmol) in ethanol (95%, 20ml) was treated with potassium hydroxide (63mg, 1.12mmol). The mixture was stirred at 22°C for 3h, and then concentrated *in vacuo*. The residue was chromatographed on silica gel [dichloromethane/methanol/ ammonium hydroxide (28%) 90 : 10 : 1 to 85 : 15 : 1] to give a white solid. Recrystallization from ethanol-water (1 : 1) afforded the title compound (300mg, 64%) as fine needles. Analysis for C₂₇H₄₂F₃NO₄·H₂O calcd. C 62.41%, H 8.54%, N 2.70%; Found: C 62.30%, H 8.70%, N 2.56%.

15

Example 69**N,N-Dimethyl-N-[2-[2-benzyl-4-(3-oxo-4,4,4-trifluorobut-1-yl)phenoxy]ethyl] dodecyl- ammonium, iodide**

20

4-[3-Benzyl-4-[2-(N-dodecyl-N-methylamino)ethoxy]phenyl]-1,1,1-trifluoro-2-butanone (180mg, 0.338mmol) was reacted by the general procedure as described in the preparation of N,N-dimethyl-N-[2-[4-(3-oxo-4,4,4-trifluorobut-1-yl)-phenoxy]ethyl] dodecyl- ammonium, iodide and afforded the title compound (228mg, 100%) as a yellow syrup. Analysis for C₃₃H₄₉F₃INO₂·1.1H₂O calcd. C 56.99%, H 7.42%, N 2.01%; Found: C 56.98%, H 7.25%, N 2.07%.

25

Example 70**N-[(Ethoxycarbonyl)methyl]-N-[2-[2-benzyl-4-(3-oxo-4,4,4-trifluorobut-1-yl)phenoxy]ethyl]-N-(methyl)- dodecylammonium, iodide**

30

4-[3-Benzyl-4-[2-(N-dodecyl-N-methylamino)ethoxy]phenyl]-1,1,1-trifluoro-2-butanone (340mg, 0.638mmol) was reacted by the general procedure as described in the preparation of N-[(ethoxycarbonyl)methyl]-

35

122

N-[2-[4-(3-oxo-4,4,4-trifluorobut-1-yl)phenoxy]ethyl]-N-(methyl)-dodecylammonium, iodide and afforded the title compound (455mg, 93%) as a yellow waxy solid.

Analysis for $C_{36}H_{53}F_3INO_4$ calcd. C 57.83%, H 7.14%, N 1.87%; Found: C 57.83%, H 7.56%, N 1.78%.

Example 71

N-(Carboxymethyl)-N-[2-[2-benzyl-4-(3-oxo-4,4,4-trifluorobut-1-yl)phenoxy]ethyl]-N-(methyl)dodecyl ammonium, hydroxide, inner salt

N-[(Ethoxycarbonyl)methyl]-N-[2-[2-benzyl-4-(3-oxo-4,4,4-trifluorobut-1-yl)phenoxy]ethyl]-N-(methyl)-dodecylammonium, iodide (330mg, 0.442mmol) was saponified as described in the preparation of N-(carboxymethyl)-N-[2-[4-(3-oxo-4,4,4-trifluorobut-1-yl)phenoxy]ethyl]-N-(methyl)dodecyl ammonium, hydroxide, inner salt, and afforded the title compound (182mg, 70%) as a white foam.

Analysis for $C_{34}H_{48}F_3NO_4 \cdot H_2O$ calcd. C 66.19%, H 8.30%, N 2.27%; Found: C 66.21%, H 8.15%, N 2.29%.

Example 72

N-[(Ethoxycarbonyl)methyl]-N-[2-[2-benzyl-4-(trifluoroacetyl)phenoxy]ethyl]-N-(methyl)-dodecylammonium, iodide

[3-Benzyl-4-[2-(N-dodecyl-N-methylamino)ethoxy]phenyl]-2,2,2-trifluoroethanone (2.81g, 5.56mmol) was reacted by the general procedure as described in the preparation of N-[(ethoxycarbonyl)methyl]-N-[2-[4-(3-oxo-4,4,4-trifluorobut-1-yl)phenoxy]ethyl]-N-(methyl)-dodecylammonium, iodide and afforded the title compound (2.1g, 52%) as a yellow solid.

Analysis for $C_{34}H_{48}F_3INO_4$ calcd. C 56.75%, H 6.86%, N 1.95%; Found: C 57.14%, H 6.94%, N 2.05%.

Example 73**N-(Carboxymethyl)-N-[2-[2-benzyl-4-(trifluoroacetyl)phenoxy]ethyl]-N-(methyl)dodecyl ammonium, hydroxide, inner salt**

5

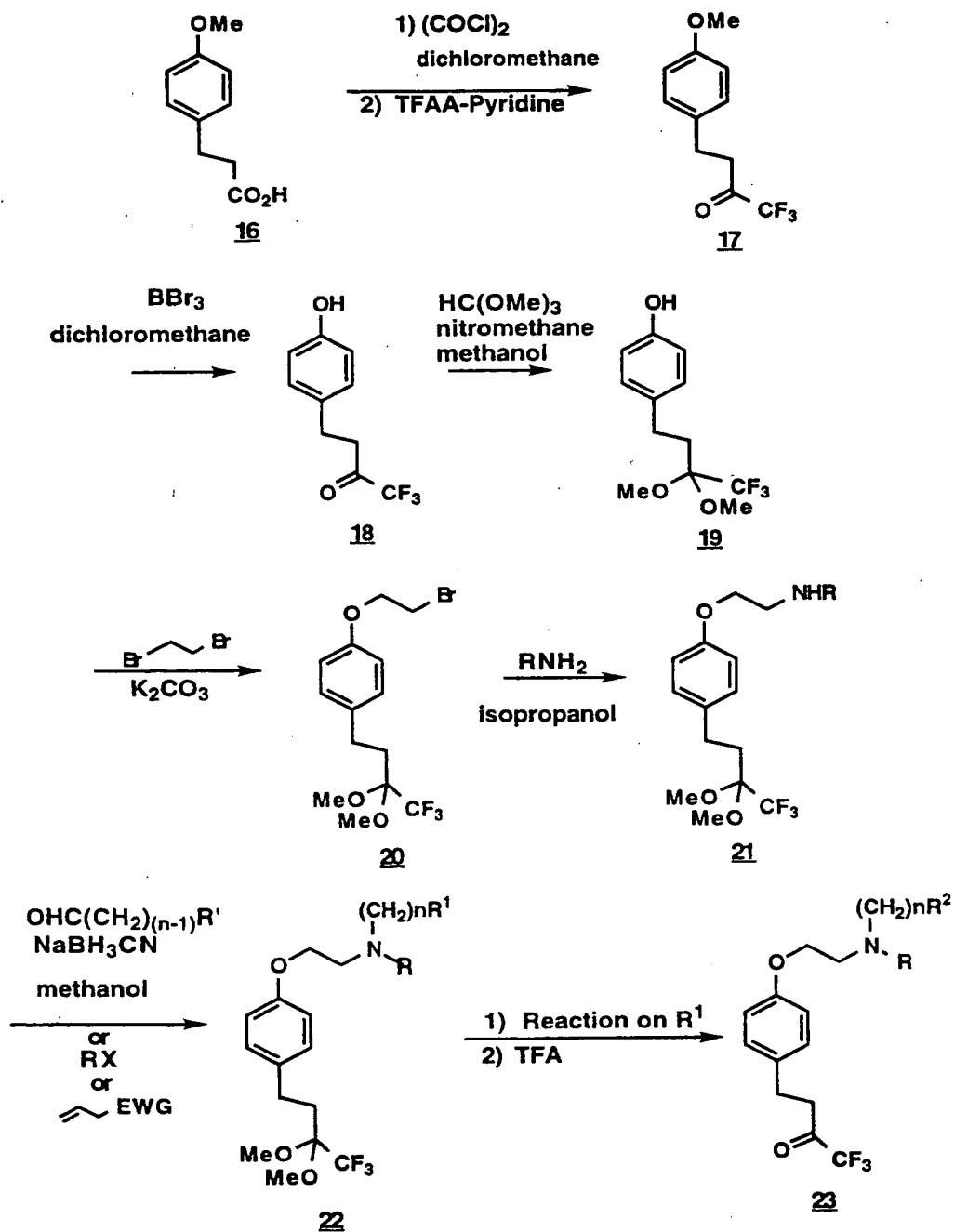
N-[(Ethoxycarbonyl)methyl]-N-[2-[2-benzyl-4-(trifluoroacetyl)phenoxy]ethyl]-N-(methyl)- dodecylammonium, iodide (500mg, 0.69mmol) was saponified as described in the preparation of N-(carboxymethyl)-N-[2-[4-(3-oxo-4,4,4-trifluorobut-1-yl)phenoxy]ethyl]-N-

10 (methyl)dodecyl ammonium, hydroxide, inner salt, and afforded the title compound (259mg, 65%) as an off-white solid.

Analysis for $C_{32}H_{44}F_3NO_4 \cdot 0.7H_2O$ calcd. C 66.69%, H 7.94%, N 2.43%;

Found: C 66.63%, H 8.00%, N 2.42%.

124

Scheme 4

125

Example 74**4-[N-Dodecyl-N-[2-[4-(3-oxo-4,4,4-trifluorobut-1-yl)phenoxy]ethyl]aminol]butanoic acid, ethyl ester**

5

Method II**4-[4-Methoxyphenyl]-1,1,1-trifluoro-2-butanone**

- 10 To a solution of 3-[4-methoxyphenyl]propionic acid (40.0g, 0.222mol) in dichloromethane (300ml) at 22°C was added slowly oxalyl chloride (29ml, 0.333mol). After stirring for 2.5h, the solvent and excess reagent were removed *in vacuo*. The residue was dissolved in dichloromethane (300ml), and was then added to a solution of trifluoroacetic anhydride
- 15 (294ml, 0.666mol) in dichloromethane (300ml) at 0°C (ice bath). Pyridine (36ml, 0.444mol) was then added dropwise at 0°C, and the reaction mixture was stirred for 0.5h at which time the cooling bath was removed. After stirring at 22°C for 3h, the reaction was cooled again to 0°C and quenched with distilled water (100ml). The mixture was stirred at 22°C for
- 20 1h, neutralized with solid sodium bicarbonate, diluted with dichloromethane (1L), washed with sat. aq. sodium bicarbonate (300ml), brine (300ml), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was purified by bulb-to-bulb distillation (96-98°C, 0.2mmHg) to afford the title compound (43.5g, 84%) as a yellow liquid.
- 25 Analysis for C₁₁H₁₁F₃O₂ calcd. C 56.90%, H 4.78%; Found: C 56.61% H 4.98%.

4-[4-Hydroxyphenyl]-1,1,1-trifluoro-2-butanone

- 30 To a solution of 1,1,1-trifluoro-4-[4-methoxyphenyl]-2-butanone (43.5g, 0.187mol) in dichloromethane (500ml) at -78°C (dry ice-acetone) was added dropwise boron tribromide (53ml, 0.561mol). The mixture was then stirred at 0°C (ice bath) for 3h, and cautiously quenched by dropwise addition of ice-water (200ml) over a period of 1h. The aqueous phase was
- 35 saturated with solid sodium chloride, extracted with dichloromethane (500ml) followed by diethyl ether (500ml). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated *in*

126

vacuo. The residue was purified by bulb-to-bulb distillation (96-100°C, 0.2mmHg) to afford the title compound (34.4g, 84%) as a yellow liquid which solidified upon standing.

Analysis for $C_{10}H_9F_3O_2 \cdot 0.5H_2O$ calcd. C 52.87%, H 4.44%; Found: C

5 52.93% H 4.53%.

4-(3,3-Dimethoxy-4,4,4-trifluorobut-1-yl)phenol

To a solution of 1,1,1-trifluoro-4-[4-hydroxyphenyl]-2-butanone (40.4g, 0.185mol) in nitromethane (300ml) were added methanol (40ml), trimethyl orthoformate (100ml) and trifluoromethanesulfonic acid (1ml). The resulting mixture was heated to 75°C for 20h, then cooled to r.t. and poured into sat. sodium bicarbonate (700ml). After stirring for 10min., the mixture was extracted with ethyl acetate (2x2L). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel (dichloromethane/methanol 98 : 2 to 97 : 3) to afford the title compound (21.5g, 44%) as a yellow oil and 1,1,1-trifluoro-4[4-hydroxyphenyl]-2-butanone (23g, 57%). Analytically pure sample (20.2g, 41%) of 4-(4,4,4-trifluoro-3,3-dimethoxybut-1-yl)phenol was obtained by bulb-to-bulb distillation (98-102°C, 0.02mmHg).

[2-[4-(3,3-Dimethoxy-4,4,4-trifluorobut-1-yl)phenoxy]ethyl] bromide

A mixture of 4-(3,3-dimethoxy-4,4,4-trifluorobut-1-yl)phenol (1.64g, 6.2mmol), potassium carbonate (1.3g, 9.3mmol) and 1,2-dibromoethane (5ml, 58mmol) was stirred and heated under reflux (130°C) for 26h. After cooling to room temperature, the mixture was filtered and washed with ethyl acetate. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography (silica gel, hexane/ethyl acetate 20 : 1 to 4 : 1) to give the title compound (2.0g, 85%) as a colorless liquid. Analysis for $C_{14}H_{18}BrF_3O_3$ calcd. C 45.30%, H 4.89%; Found: C 45.57% H 4.72%.

(27)

N-[2-[4-(3,3-Dimethoxy-4,4,4-trifluorobut-1-yl)phenoxy]ethyl]dodecanamine

- A mixture of 4-[4-(2-bromoethoxy)phenyl]-1,1,1-trifluoro-2-butanone, dimethyl ketal (5.0g, 13.5mmol), dodecylamine (12.5g 67.4mmol), disopropylethylamine (7.0ml, 40.4mmol), NaI (2.0g, 13.5mmol) and isopropanol(100ml) was stirred and heated under reflux for 16h. After cooling to room temperature, the mixture was concentrated *in vacuo*, diluted with ethyl acetate (300ml), washed with brine (100ml), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel (dichloromethane/methanol 98 : 2 to 96 : 4) to afford the title compound (5.3g, 83%) as a colorless syrup. Treatment of the above free amine with anhydrous hydrogen chloride (1.0 M in ether) gave the hydrochloride salt as a white solid.
- Analysis for $C_{26}H_{44}F_3N O_3 \cdot HCl$ calcd. C 60.98%, H 8.86%, N 2.74%;
Found: C 60.73% H 8.56% N 2.73%.

4-[N-Dodecyl-N-[2-[4-(3,3-Dimethoxy-4,4,4-trifluorobut-1-yl)phenoxy]ethyl]amino]butanoic acid, ethyl ester

- A solution of N-[2-[4-(3,3-dimethoxy-4,4,4-trifluorobut-1-yl)phenoxy]ethyl]dodecanamine (2.0g, 4.2mmol) in methanol (50ml) was treated with sodium cyanoborohydride (0.55g, 8.4mmol) and ethyl 4-oxobutyrates (1.04g, 8.4mmol). The resulting mixture was stirred at 22°C for 16h, diluted with diethyl ether (350ml), washed with water (200ml), brine (200ml), dried over magnesium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane/AcOEt 9 : 1 to 6 : 1) to afford the title compound (1.8g, 73%) as a liquid.
- Analysis for $C_{32}H_{54}F_3N O_5 \cdot 0.3H_2O$ calcd. C 64.58%, H 9.25%, N 2.35%;
Found: C 64.54% H 9.02% N 2.39%.

4-[N-Dodecyl-N-[2-[4-(3-oxo-4,4,4-trifluorobut-1-yl)phenoxy]ethyl]amino]butanoic acid, ethyl ester

- A solution of 4-[N-Dodecyl-N-[2-[4-(3,3-dimethoxy-4,4,4-trifluorobut-1-yl)phenoxy]ethyl]amino]- butanoic acid, ethyl ester (315mg, 0.53mmol) in trifluoroacetic acid (5ml) was heated to 70°C for 2h, and then concentrated

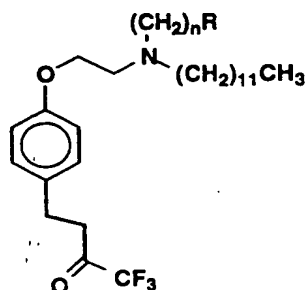
128

in vacuo . The residue was diluted with ethyl acetate (100ml), washed with sat. sodium bicarbonate (30ml), brine (30ml), dried over magnesium sulfate and concentrated *in vacuo* . The residue was chromatographed on silica gel (Hexane/ethyl acetate 2 : 1 to 1.5 : 1) to afford the title compound
5 (224mg, 77%) as a colorless oil.

The following compounds may be prepared by the general procedure of Scheme 4.

129

SCHEME 4 Table



5

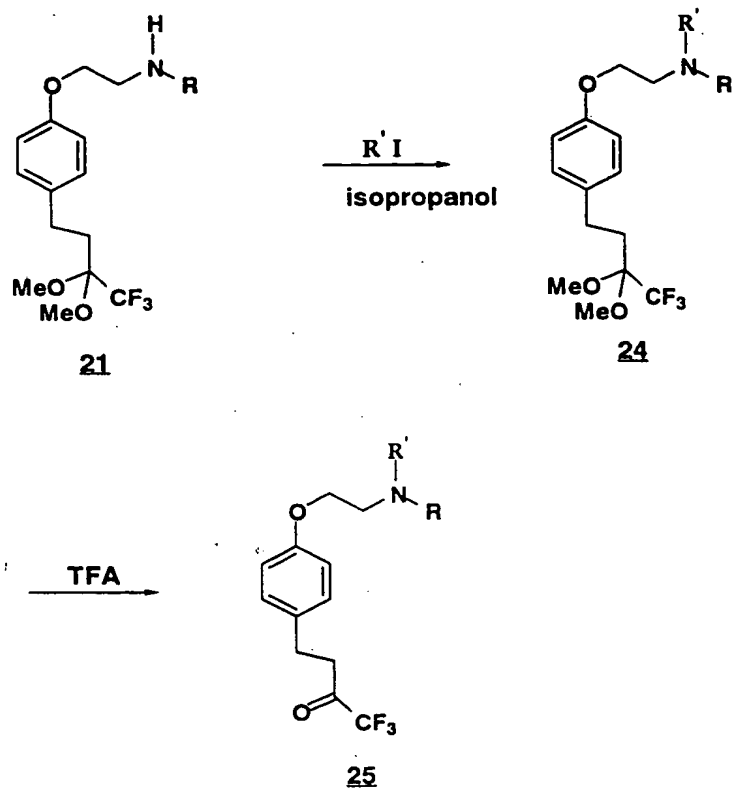
Example No.	n	R	Analysis
75	0	H	C ₂₄ H ₃₈ F ₃ NO ₄ . H ₂ O.0.3 CO ₂ Calcd: C 63.34, H 8.75, N 3.04 Found: C 63.66, H 8.36, N 3.19
76	1	CH(CH ₃) ₂	C ₂₈ H ₄₆ F ₃ NO ₂ . HCl.0.6 H ₂ O Calcd: C 63.10, H 9.12, N 2.63 Found: C 62.92, H 9.18, N 2.68
77	1	C(CH ₃) ₃	C ₂₉ H ₄₈ F ₃ NO ₂ . HCl .0.6 H ₂ O Calcd: C 63.68, H 9.25, N 2.56 Found: C 63.51, H 8.91, N 2.61
78	4	CONHEt	C ₃₁ H ₅₁ F ₃ N ₂ O ₃ . HCl .1.8 H ₂ O Calcd: C 59.51, H 8.96, N 4.48 Found: C 59.48, H 8.70, N 4.50
79	3	CONHEt	C ₃₀ H ₄₉ F ₃ N ₂ O ₃ . HCl .1.1 H ₂ O Calcd: C 60.15, H 8.78, N 4.68 Found: C 60.15, H 8.54, N 4.63
80	5	OH	C ₂₉ H ₄₈ F ₃ NO ₃ . HCl .0.6 H ₂ O Calcd: C 61.87, H 8.99, N 2.49 Found: C 61.81, H 8.58, N 2.66

130

81	4	OH	$C_{28}H_{46}F_3NO_3 \cdot HCl \cdot 0.5 H_2O$ Calcd: C 61.47, H 8.84, N 2.56 Found: C 61.44, H 8.91, N 2.67
82	3	OCH ₃	$C_{28}H_{46}F_3NO_3 \cdot HCl \cdot 1.2 H_2O$ Calcd: C 60.08, H 8.90, N 2.50 Found: C 60.08, H 8.46, N 2.77
83	2	CN	$C_{27}H_{41}F_3N_2O_3 \cdot HCl \cdot 0.8 H_2O$ Calcd: C 60.79, H 8.24, N 5.25 Found: C 60.75, H 8.16, N 5.23

151

Scheme 5



Example 84**4-[4-[2-(N-Dodecyl-N-propylamino)ethoxy]phenyl]-1,1,1-trifluoro-2-butanone**

5

N-Propyl-N-[2-[4-(3,3-dimethoxy-4,4,4-trifluorobut-1-yl)phenoxy]ethyl]dodecylamine

A solution of N-[2-[4-(3,3-dimethoxy-4,4,4-trifluorobut-1-yl)phenoxy]ethyl]dodecylamine (500mg, 1.05mmol), diisopropyl ethylamine (0.35ml, 2.1mmol) and 1-iodopropane (0.26ml, 2.66mmol) in isopropanol was heated to reflux for 21 h. After cooling to r.t., the mixture was diluted with ethyl acetate and filtered. The filtrate was concentrated *in vacuo*, and the residue was chromatographed on silica gel (dichloromethane/methanol 98 : 2 to 95 : 5) to afford the title compound (0.526g, 73%) as a colorless oil.

15

4-[4-[2-(N-Dodecyl-N-propylamino)ethoxy]phenyl]-1,1,1-trifluoro-2-butanone

20

N-Propyl-N-[2-[4-(4,4,4-trifluoro-3,3-dimethoxybut-1-yl)phenoxy]ethyl]dodecylamine (300mg, 0.58mmol) was treated with trifluoroacetic acid as described in the preparation of 4-[N-dodecyl-N-[2-[4-(4,4,4-trifluoro-3-oxobut-1-yl)phenoxy]ethyl]amino]butanoic acid, ethyl ester and afforded the title compound (169mg, 62%) as a pale yellow oil. Analysis for C₂₇H₄₄F₃NO₂·0.9H₂O calcd. C 66.47%, H 9.46%, N 2.87%; Found: C 66.39%, H 9.10%, N 2.87%. Treatment of the above free amine with anhydrous hydrogen chloride (1.0 M in ether) gave the hydrochloride salt as a pale yellow syrup. Analysis for C₂₇H₄₄F₃NO₂·HCl·1.2H₂O calcd. C 61.22%, H 9.02%, N 2.64%; Found: C 61.38%, H 8.61%, N 2.75%.

25

30

35

Example 85**4-[4-[2-(N-Dodecyl-N-hexylamino)ethoxy]phenyl]-1,1,1-trifluoro-2-butanone**

5

N-Hexyl-N-[2-[4-(3,3-dimethoxy-4,4,4-trifluorobut-1-yl)phenoxy]ethyl]dodecylamine

10 N-[2-[4-(3,3-Dimethoxy-4,4,4-trifluorobut-1-yl)phenoxy]ethyl]dodecylamine (500mg, 1.05mmol) and 1-iodohexane (0.186ml, 1.26mmol) were reacted as described in the preparation of N-propyl-N-[2-[4-(3,3-dimethoxy-4,4,4-trifluorobut-1-yl)phenoxy]ethyl]dodecylamine and afforded the title compound (390mg, g, 67%) as a liquid.

15

4-[4-[2-(N-Dodecyl-N-Hexylamino)ethoxy]phenyl]-1,1,1-trifluoro-2-butanone

20 N-Hexyl-N-[2-[4-(3,3-dimethoxy-4,4,4-trifluorobut-1-yl)phenoxy]ethyl]dodecylamine (353mg, 0.63mmol) was treated with trifluoroacetic acid as described in the preparation of 4-[N-dodecyl-N-[2-[4-(4,4,4-trifluoro-3-oxobut-1-yl)phenoxy]ethyl]amino]butanoic acid, ethyl ester. The residue was chromatographed on silica gel (dichloromethane/methanol 98 : 2 to 94 : 6) to afford the title compound (253mg, 78%) as a pale yellow oil.

25

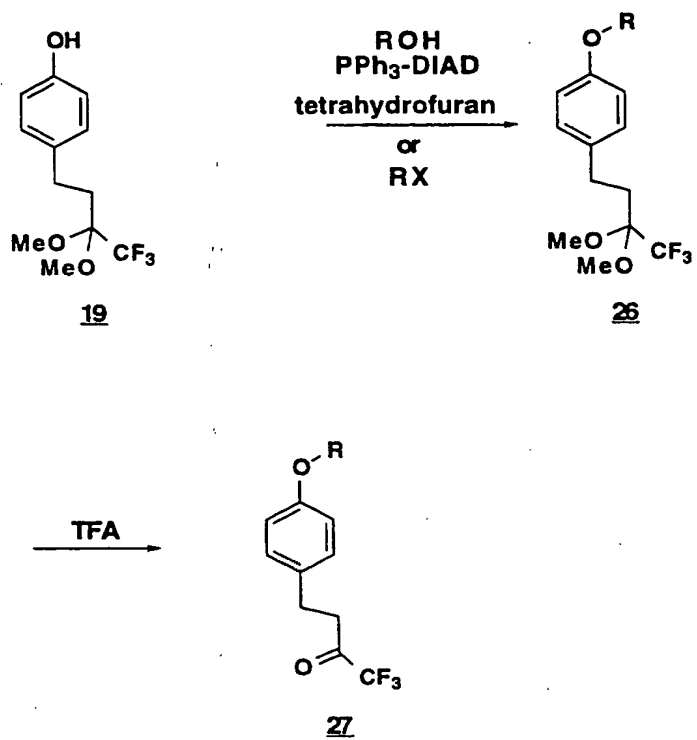
Analysis for C₃₀H₅₀F₃NO₂ calcd. C 70.14%, H 9.81%, N 2.73%; Found: C 69.79%, H 9.82%, N 2.76%.

Treatment of the above free amine with anhydrous hydrogen chloride (1.0 M in ether) gave the hydrochloride salt as a pale yellow syrup.

30

Analysis for C₃₀H₅₀F₃NO₂·HCl·0.7H₂O calcd. C 64.02%, H 9.39%, N 2.49%; Found: C 64.09%, H 9.05%, N 2.61%.

134

Scheme 6

Example 86**4-[4-[2-(N-dodecyl-N-ethylamino)ethoxy]phenyl]-1,1,1-trifluoro-2-butanone**

5

2-[N-Dodecyl-N-ethylamino]ethanol

2-[Dodecylamino]ethanol (2.0g, 8.73 mmol) ,1-iodoethane (1.63g, 10.48 mmol) and N,N-diisopropylethylamine (2.51g,17.5 mmol) in
10 isopropanol (25 ml)were heated under reflux for 4 h. The solvent was then evaporated *in vacuo* and the residue was diluted with ethyl acetate washed with aqueous sodium bicarbonate, brine and dried (magnesium sulfate). Evaporation of the solvent followed by
15 chromatography on silica gel (ethyl acetate/methanol 90 : 10 to 80 : 20) afforded the title compound (1.65g, 73%) as a white solid.

N-Ethyl-N-[2-[4-(3,3-dimethoxy-4,4,4-trifluoro-but-1-yl)phenoxy]ethyl]dodecylamine

20 2-[N-Dodecyl-N-ethylamino]ethanol (250mg, 0.96mmol) and 4-(3,3-dimethoxy-4,4,4-trifluorobut-1-yl)phenol (230mg, 0.87mmol) were reacted under Mitsunobu conditions as described in the preparation of 3-[4-[2-(N-dodecyl-N-methylamino)ethoxy]phenyl]propanoic acid, methyl ester. The usual work-up followed by chromatography on silica gel (Hexane/ethyl
25 acetate 95 : 5 to 80 : 20) afforded the title compound (200mg, 46%) as a colorless oil.

4-[4-[2-(N-dodecyl-N-ethylamino)ethoxy]phenyl]-1,1,1-trifluoro-2-butanone

30

N-Ethyl-N-[2-[4-(3,3-dimethoxy-4,4,4-trifluorobut-1-yl)phenoxy]ethyl]dodecylamine (123mg, 0.244mmol) was treated with trifluoroacetic acid as described in the preparation of 4-[N-dodecyl-N-[2-[4-(4,4,4-trifluoro-3-oxobut-1-yl)phenoxy]ethyl]amino]butanoic acid, ethyl
35 ester and afforded the title compound (60mg, 54%) as a pale yellow oil. Treatment of the above free amine with anhydrous hydrogen chloride (1.0 M in ether) gave the hydrochloride salt as a pale yellow syrup.

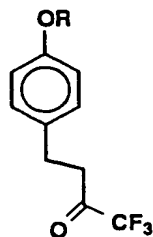
136

Analysis for $C_{26}H_{42}F_3NO_2 \cdot HCl \cdot 0.6H_2O$ calcd. C 60.45%, H 8.64%, N 2.69%;
Found: C 60.19%, H 8.27%, N 3.08%.

- 5 The following compounds may be prepared by the general
procedure of Scheme 6.

137

SCHEME 6 Tables

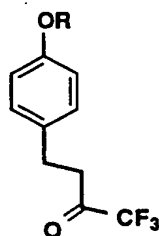


Exp. #	R	Analysis
87	$\text{CH}_2\text{CH}_2\text{N} \begin{cases} (\text{CH}_2)_5\text{CH}_3 \\ (\text{CH}_2)_5\text{CH}_3 \end{cases}$	$\text{C}_{24}\text{H}_{38}\text{F}_3\text{NO}_2 \cdot \text{HCl} \cdot 1.4 \text{ H}_2\text{O}$ Calcd: C 58.68, H 8.58, N 2.85 Found: C 58.81, H 8.45, N 2.91
88	$\text{CH}_2\text{CH}_2\text{N} \begin{cases} (\text{CH}_2)_7\text{CH}_3 \\ (\text{CH}_2)_7\text{CH}_3 \end{cases}$	$\text{C}_{28}\text{H}_{46}\text{F}_3\text{NO}_2 \cdot \text{HCl} \cdot 0.8 \text{ H}_2\text{O}$ Calcd: C 62.68, H 9.18, N 2.61 Found: C 62.52, H 9.25, N 2.69
89	$\text{CH}_2\text{CH}_2\text{N} \begin{cases} \text{CH}_2\text{C}_6\text{H}_5 \\ \text{CH}_2\text{C}_6\text{H}_5 \end{cases}$	$\text{C}_{26}\text{H}_{26}\text{F}_3\text{NO}_2 \cdot \text{HCl} \cdot 0.8 \text{ H}_2\text{O}$ Calcd: C 63.43, H 5.86, N 2.84 Found: C 63.39, H 5.95, N 2.88
90		$\text{C}_{26}\text{H}_{24}\text{Cl}_2\text{F}_3\text{NO}_2 \cdot \text{HCl} \cdot 0.7 \text{ H}_2\text{O}$ Calcd: C 55.82, H 4.76, N 2.50 Found: C 55.81, H 4.90, N 2.52
91	$\text{CH}_2\text{CH}_2\text{N} \begin{matrix} \text{---} \text{C}_6\text{H}_{11} \text{---} \end{matrix} \text{CH}_2 \text{---} \text{C}_6\text{H}_5$	$\text{C}_{24}\text{H}_{28}\text{F}_3\text{NO}_2 \cdot \text{HCl} \cdot 0.9 \text{ H}_2\text{O}$ Calcd: C 61.05, H 6.58, N 2.97 Found: C 61.17, H 6.54, N 3.05

92	$\text{CH}_2\text{CH}_2\text{-N} \begin{array}{c} \diagup \diagdown \\ \text{---} \end{array} \text{O}(\text{CH}_2)_7\text{CH}_3$	$\text{C}_{25}\text{H}_{38}\text{F}_3\text{NO}_3 \cdot \text{HCl} \cdot 0.7 \text{H}_2\text{O}$ Calcd: C 59.27, H 8.04, N 2.76 Found: C 59.26, H 8.18, N 2.98
93	$\text{CH}_2\text{CH}_2\text{-N} \begin{array}{c} \text{CH}_3 \\ \end{array} \text{-(CH}_2)_3\text{O} \text{---} \text{C}_6\text{H}_4 \text{---} \text{CH}_2 \text{---} \text{C}_6\text{H}_5$	$\text{C}_{29}\text{H}_{32}\text{F}_3\text{NO}_3 \cdot \text{HCl} \cdot 0.9 \text{H}_2\text{O}$ Calcd: C 63.07, H 6.35, N 2.54 Found: C 62.95, H 6.40, N 2.67
94	$\text{CH}_2\text{CH}_2\text{-N} \begin{array}{c} \text{CH}_3 \\ \end{array} \text{-(CH}_2)_3 \text{---} \text{C}_6\text{H}_4 \text{---} \text{O} \text{---} \text{CH}_2 \text{---} \text{CH(CH}_3)_2$	$\text{C}_{26}\text{H}_{34}\text{F}_3\text{NO}_3 \cdot \text{HCl} \cdot \text{H}_2\text{O}$ Calcd: C 60.05, H 7.17, N 2.69 Found: C 60.03, H 7.26, N 2.79
95	$\text{CH}_2\text{CH}_2\text{-N} \begin{array}{c} \text{CH}_3 \\ \end{array} \text{-(CH}_2)_3\text{O} \text{---} \text{C}_6\text{H}_4 \text{---} \text{O} \text{---} \text{CH(CH}_3)_2$	$\text{C}_{25}\text{H}_{32}\text{F}_3\text{NO}_3 \cdot \text{HCl} \cdot 0.6 \text{H}_2\text{O}$ Calcd: C 60.20, H 6.91, N 2.81 Found: C 60.11, H 7.11, N 2.89
96	$(\text{CH}_2)_{11}\text{CH}_3$	$\text{C}_{22}\text{H}_{33}\text{F}_3\text{O}_2$ Calcd: C 68.37, H 8.61 Found: C 68.09, H 8.42
97	$(\text{CH}_2)_{14}\text{CH}_3$	$\text{C}_{25}\text{H}_{29}\text{F}_3\text{O}_2 \cdot \text{H}_2\text{O}$ Calcd: C 69.48, H 9.19 Found: C 69.37, H 9.29
98	$\text{CH}_2\text{CH}_2\text{O}(\text{CH}_2)_{11}\text{CH}_3$	$\text{C}_{24}\text{H}_{37}\text{F}_3\text{O}_3$ Calcd: C 66.95, H 8.66 Found: C 66.76, H 8.47
99	$\text{CH}_2\}_2 \text{ (dimer)}$	$\text{C}_{22}\text{H}_{20}\text{F}_6\text{O}_4 \cdot 0.5 \text{H}_2\text{O}$ Calcd: C 56.06, H 4.49 Found: C 56.11, H 4.45
100	$\text{CH}_2 \text{---} \text{C}_6\text{H}_5$	$\text{C}_{17}\text{H}_{15}\text{F}_3\text{O}_2$ Calcd: C 66.23, H 4.90 Found: C 66.25, H 4.99
101	$\text{CH}_2\text{CH}_2\text{Br}$	$\text{C}_{12}\text{H}_{12}\text{BrF}_3\text{O}_2$ Calcd: C 44.33, H 3.72 Found: C 44.71, H 3.80

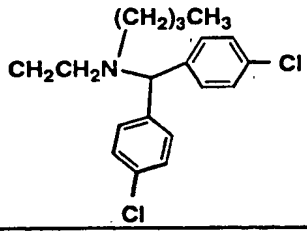
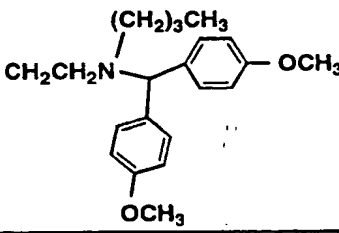
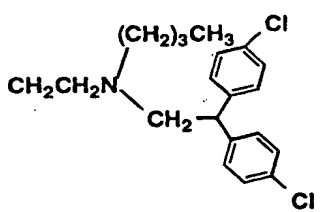
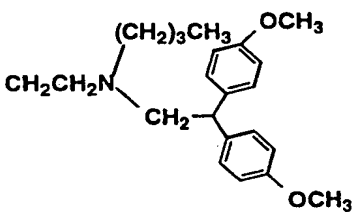
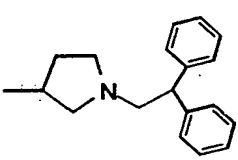
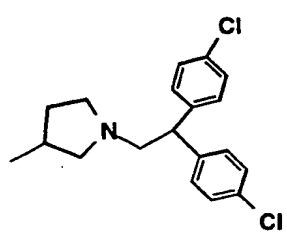
139

SCHEME 6 - Table (continued)

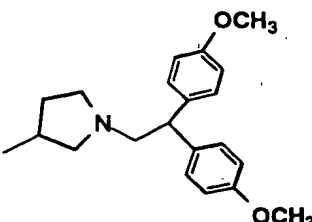
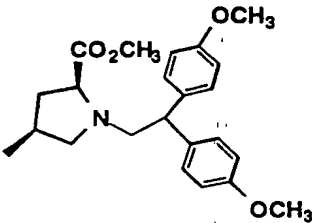
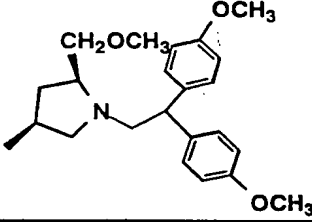
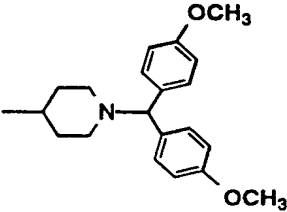
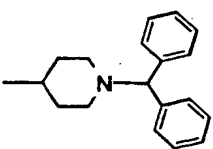
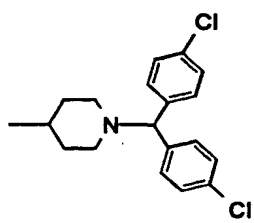


Exp. #	R	Analysis
102		<p>$C_{20}H_{16}F_3NO_2 \cdot HCl \cdot 0.8 H_2O$</p> <p>Calcd: C 58.56, H 4.57, N 3.41</p> <p>Found: C 58.31, H 4.19, N 3.45</p>
103		<p>$C_{26}H_{39}F_3O_3 \cdot 0.3 H_2O$</p> <p>Calcd: C 67.60, H 8.64</p> <p>Found: C 67.55, H 8.45</p>
104		<p>$C_{26}H_{19}Cl_2F_3N_2O_2$</p> <p>Calcd: C 60.13, H 3.69, N 5.39</p> <p>Found: C 60.37, H 3.71, N 5.39</p>
105		<p>$C_{29}H_{26}Cl_2F_3N_3O_2 \cdot HCl \cdot 1.1 H_2O$</p> <p>Calcd: C 55.05, H 4.65, N 6.64</p> <p>Found: C 54.96, H 4.61, N 6.62</p>

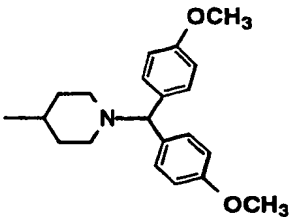
40

106		$C_{29}H_{30}Cl_2F_3NO_2 \cdot HCl \cdot 0.7 H_2O$ Calcd: C 57.91, H 5.43, N 2.33 Found: C 57.98, H 5.42, N 2.12
107		$C_{31}H_{36}F_3NO_4 \cdot HCl \cdot 0.7 H_2O$ Calcd: C 62.82, H 6.53, N 2.36 Found: C 62.87, H 6.33, N 2.08
108		$C_{30}H_{32}Cl_2F_3NO_2 \cdot HCl \cdot 0.6 H_2O$ Calcd: C 58.71, H 5.62, N 2.28 Found: C 58.64, H 5.51, N 2.33
109		$C_{32}H_{38}F_3NO_4 \cdot HCl \cdot H_2O$ Calcd: C 62.79, H 6.75, N 2.29 Found: C 62.81, H 6.82, N 2.15
110		$C_{28}H_{28}F_3NO_2 \cdot HCl \cdot 0.3 H_2O$ Calcd: C 66.02, H 5.86, N 2.75 Found: C 65.93, H 5.98, N 2.74
111		$C_{28}H_{26}Cl_2F_3NO_2 \cdot HCl \cdot H_2O$ Calcd: C 56.84, H 4.77, N 2.36 Found: C 56.76, H 4.88, N 2.42

141

112		$C_{30}H_{32}F_3NO_4 \cdot HCl \cdot 0.9 H_2O$ Calcd: C 62.10, H 6.05, N 2.41 Found: C 62.11, H 6.33, N 2.48
113		$C_{32}H_{34}F_3NO_6 \cdot HCl \cdot 2.5 H_2O$ Calcd: C 57.61, H 6.04, N 2.10 Found: C 57.56, H 5.44, N 2.11
114		$C_{32}H_{36}F_3NO_5 \cdot HCl \cdot 1.5 H_2O$ Calcd: C 60.52, H 6.35, N 2.21 Found: C 60.49, H 6.34, N 2.17
115		$C_{30}H_{32}F_3NO_4 \cdot HCl \cdot 0.7 H_2O$ Calcd: C 62.49, H 6.01, N 2.43 Found: C 62.36, H 6.00, N 2.36
116		$C_{29}H_{30}F_3NO_2 \cdot HCl \cdot 2 H_2O$ Calcd: C 62.87, H 6.37, N 2.53 Found: C 62.89, H 6.02, N 2.62
117		$C_{29}H_{28}Cl_2F_3NO_2 \cdot HCl \cdot 1.6 H_2O$ Calcd: C 56.57, H 5.27, N 2.27 Found: C 56.2, H 4.86, N 2.25

142

118	 The structure shows a piperazine ring with a methyl group on one of the carbons adjacent to the nitrogen. The nitrogen is substituted with a 4-methoxyphenyl group. Another 4-methoxyphenyl group is attached to the carbon adjacent to the nitrogen, forming a biphenyl-like system.	$C_{31}H_{34}F_3NO_4 \cdot HCl \cdot 0.9 H_2O$ Calcd: C 62.65, H 6.24, N 2.36 Found: C 62.58, H 6.15, N 2.42
-----	--	--

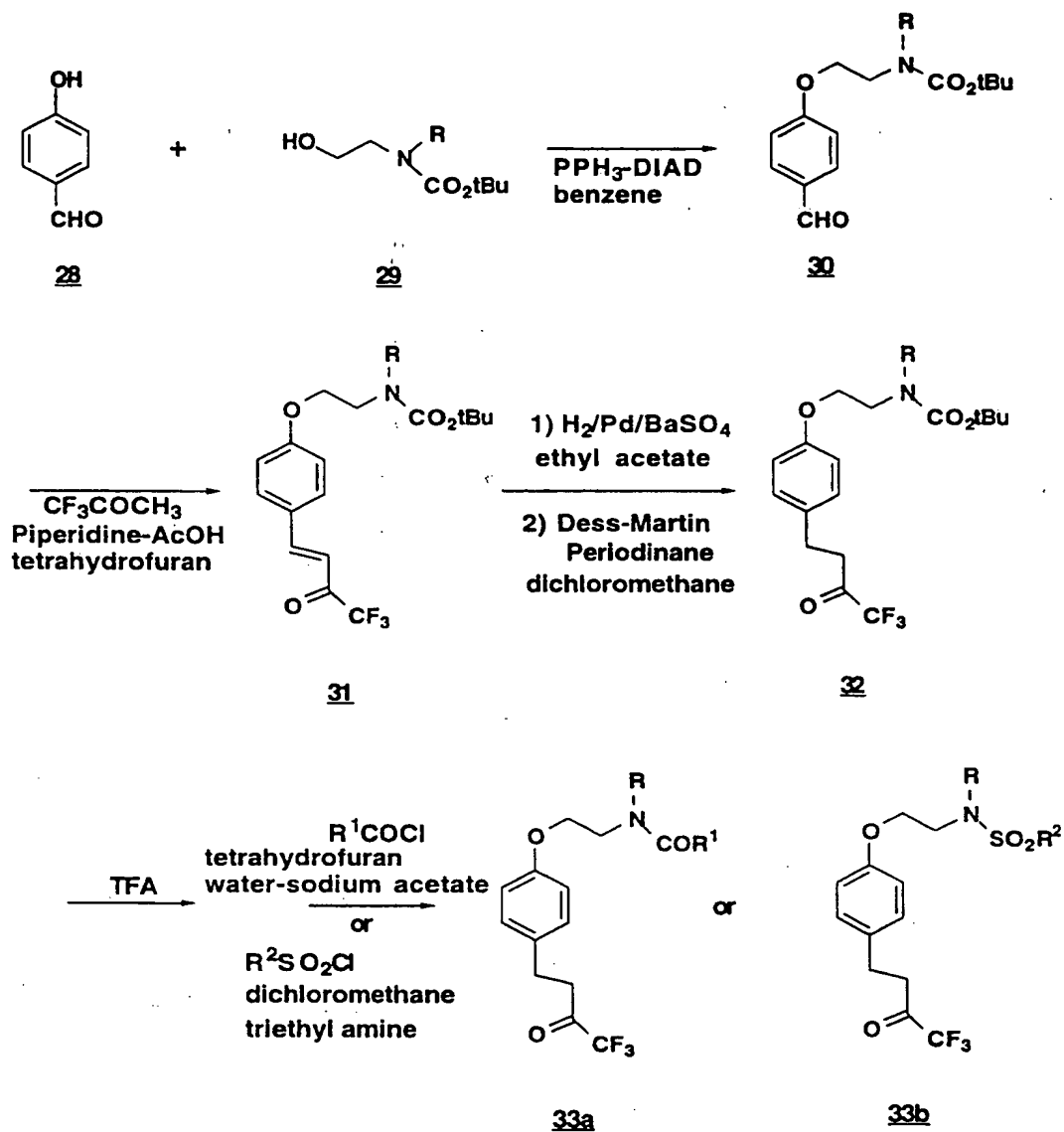
5

10

15

20

143

Scheme 7

Example 119**N-[2-[4-(4,4,4-trifluoro-3-oxo-1-butyl)phenoxy]ethyl]-N-methyl
dodecanamide**

5

N-[2-(4-formylphenoxy)ethyl]-N-methylcarbamic acid, 1,1-dimethylethyl ester

10 A solution of N-(2-hydroxyethyl)-N-methylcarbamic acid, 1,1-dimethylethyl ester (7.05 g, 40.2 mmol; W.S. Saari and all, J. Med. Chem. 33, 97 (1990)), 4-hydroxybenzaldehyde (3.75 g, 30.7 mmol) and triphenylphosphine (10.57 g, 40.3 mmol) in dry benzene (120 ml) was cooled to 15°C and treated with diisopropyl azodicarboxylate (8.15 g, 40.3 mmol) in dry benzene (20 ml) added dropwise over 20 min. After 16 h at 15 22°C, and chromatography on silica gel (elution toluene-ethyl acetate 9:1-8:2) gave 4.40 g (52%) of the title material as white cubes: mp 62-65°C (ether-hexane).

Anal. Calcd. for C₁₅H₂₁N₀₄: C 64.50, H 7.58, N 5.01.

Found: C 64.25, H 7.59, N 5.00.

20

E-N-[2-[4-(4-trifluoro-3-oxo-1-butenyl)phenoxy]ethyl]-N-methylcarbamic acid, 1,1-dimethylethyl ester

25 A solution of N-[2-(4-formylphenoxy)ethyl]-N-methylcarbamic acid, 1,1-dimethylethyl ester (3.72 g, 13.3 mmol) in dry tetrahydrofuran (65 ml) was cooled to 10°C and treated with acetic acid (1.4 ml) and piperidine (1.4 ml). Then 1,1,1-trifluoroacetone (7 ml) in dry tetrahydrofuran was added dropwise over 10 min. After 2 h and 4 h at 20°C, two other successive portions of 1,1,1-trifluoromethylacetone (2 x 7 ml) were also added. After 30 another 2 h at 22°C, the reaction mixture was diluted with ethyl acetate (300 ml) washed with water, saturated ammonium chloride, saturated sodium bicarbonate and brine. The organic phase was then dried, concentrated and chromatographed on silica gel. Elution with a gradient of ethyl acetate in hexane (0 - 20%) gave 3.05 g (61%) of the title material as 35 yellow crystals: mp 76-77°C (hexane).

Anal. Calcd. for C₁₈H₂₂N₀₄F₃: C 57.90, H 5.94, N 3.75.

145

Found: C 57.82, H 5.92, N 3.72.

N-[2-[4-(4-trifluoro-3-oxo-1-butyl)phenoxy]ethyl]-N-methylcarbamic acid, 1,1-dimethylethyl ester

5

A solution of (E)-N-[2-[4-(4-trifluoro-3-oxo-1-butenyl)phenoxy]ethyl]-N-methylcarbamic acid, 1,1-dimethylethyl ester (1.10 g, 2.95 mmol) in ethyl acetate (80 ml) was hydrogenated at atmospheric pressure over 5% palladium on barium sulfate (0.20 g) for 1 hour. The catalyst was then
10 filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in dichloromethane (60 ml) and then treated at 22°C with Dess-Martin periodinane reagent (2.50 g, 5.90 mmol). After 1 hour, the reaction mixture was diluted with ethyl acetate, washed with 10% aqueous sodium thiosulfate and saturated sodium bicarbonate. After
15 drying, the organic phase was concentrated and chromatographed on silica gel. Elution with a gradient of ethyl acetate (0 - 10%) in toluene gave 0.880 g (79%) of the title material as an amorphous solid. By ¹H NMR this product is a mixture of ketone and hydrated ketone.

Anal. Calcd. for C₁₈H₂₄N₀₄F₃. 0.7 H₂O: C 55.72, H 6.60, N 3.61.

20 Found: C 55.80, H 6.52, N 3.52.

N-[2-[4-(4-trifluoro-3-oxo-1-butyl)phenoxy]ethyl]-N-methyldodecanamide

A solution of N-[2-[4-(4-trifluoro-3-oxo-1-butyl)phenoxy]ethyl]-N-methylcarbamic acid, 1,1-dimethylethyl ester (0.200 g, 0.53 mmol) in
25 dichloromethane (10 ml) was treated with trifluoroacetic acid (1 ml) and stirred at 22°C for 1 h. The solvent was evaporated *in vacuo* and the residue was co-evaporated with toluene three times. The product was then dissolved in tetrahydrofuran (10 ml) treated with 40% sodium
30 acetate in water (10 ml) and while stirred vigorously treated with lauroyl chloride (0.116 g, 0.53 g mmol) added dropwise over 2 min. After 1 hour at 22°C, the reaction mixture was diluted with ethyl acetate (150 ml), washed with water, saturated sodium bicarbonate and brine. After drying (magnesium sulfate) the solvent was evaporated *in vacuo* and the
35 residue was chromatographed on silica gel. Elution with a gradient of ethyl acetate (0 - 30%) in toluene gave 0.181 g (74%) of the title material as

146

a waxy solid. By ^1H NMR, this product is a mixture of ketone and hydrated ketone.

Anal. Calcd. for $\text{C}_{25}\text{H}_{38}\text{F}_3\text{N}_3 \cdot \text{H}_2\text{O}$: C 63.14, H 8.48, N 2.95.

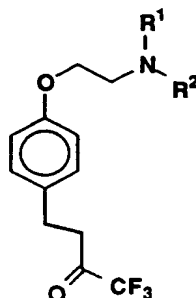
Found: C 63.26, H 8.03, N 2.87.

5

The following compounds may be prepared by the general procedure of Scheme 7.

147

SCHEME 7



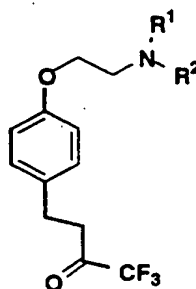
Exp. #	R ¹	R ²	Analysis
120	H		C ₂₄ H ₃₆ F ₃ NO ₃ · 0.2 H ₂ O Calcd: C 64.47, H 8.21, N 3.13 Found: C 64.47, H 8.03, N 3.09
121	CH ₃		C ₂₇ H ₂₄ Cl ₂ F ₃ NO ₃ · H ₂ O Calcd: C 58.28, H 4.71, N 2.52 Found: C 58.43, H 4.38, N 2.64
122	(CH ₂) ₁₁ CH ₃	COCH ₃	C ₂₆ H ₄₀ F ₃ NO ₃ · 1.7 H ₂ O Calcd: C 62.18, H 8.71, N 2.79 Found: C 61.95, H 8.51, N 2.83
123	(CH ₂) ₁₁ CH ₃	CO ₂ tBu	C ₂₉ H ₄₆ F ₃ NO ₄ Calcd: C 64.66, H 8.79, N 2.60 Found: C 64.81, H 8.79, N 2.70
124	H	CO ₂ tBu	C ₁₇ H ₂₂ F ₃ NO ₄ Calcd: C 56.51, H 6.14, N 3.88 Found: C 56.35, H 6.19, N 3.84

148

125	H	$\text{SO}_2(\text{CH}_2)_6\text{CH}_3$	$\text{C}_{19}\text{H}_{28}\text{F}_3\text{NO}_4\text{S} \cdot 0.2 \text{ H}_2\text{O}$ Calcd: C 53.43, H 6.70, N 3.28, S 7.51 Found: C 53.43, H 6.72, N 3.28, S 7.50
126	H	$\text{SO}_2(\text{CH}_2)_{11}\text{CH}_3$	$\text{C}_{24}\text{H}_{38}\text{F}_3\text{NO}_4\text{S}$ Calcd: C 58.40, H 7.76, N 2.84, S 6.50 Found: C 58.29, H 7.77, N 2.84, S 6.40
127	CH_3	$\text{SO}_2(\text{CH}_2)_{11}\text{CH}_3$	$\text{C}_{25}\text{H}_{40}\text{F}_3\text{NO}_4\text{S}$ Calcd: C 59.15, H 7.94, N 2.76, S 6.32 Found: C 59.02, H 7.70, N 2.79, S 6.25
128	H	$\text{CSNH}(\text{CH}_2)_9\text{CH}_3$	$\text{C}_{23}\text{H}_{35}\text{F}_3\text{N}_2\text{O}_2\text{S}$ Calcd: C 59.98, H 7.66, N 6.08, S 6.96 Found: C 59.80, H 7.70, N 6.05, S 7.06

149

SCHEME 7 (continued)

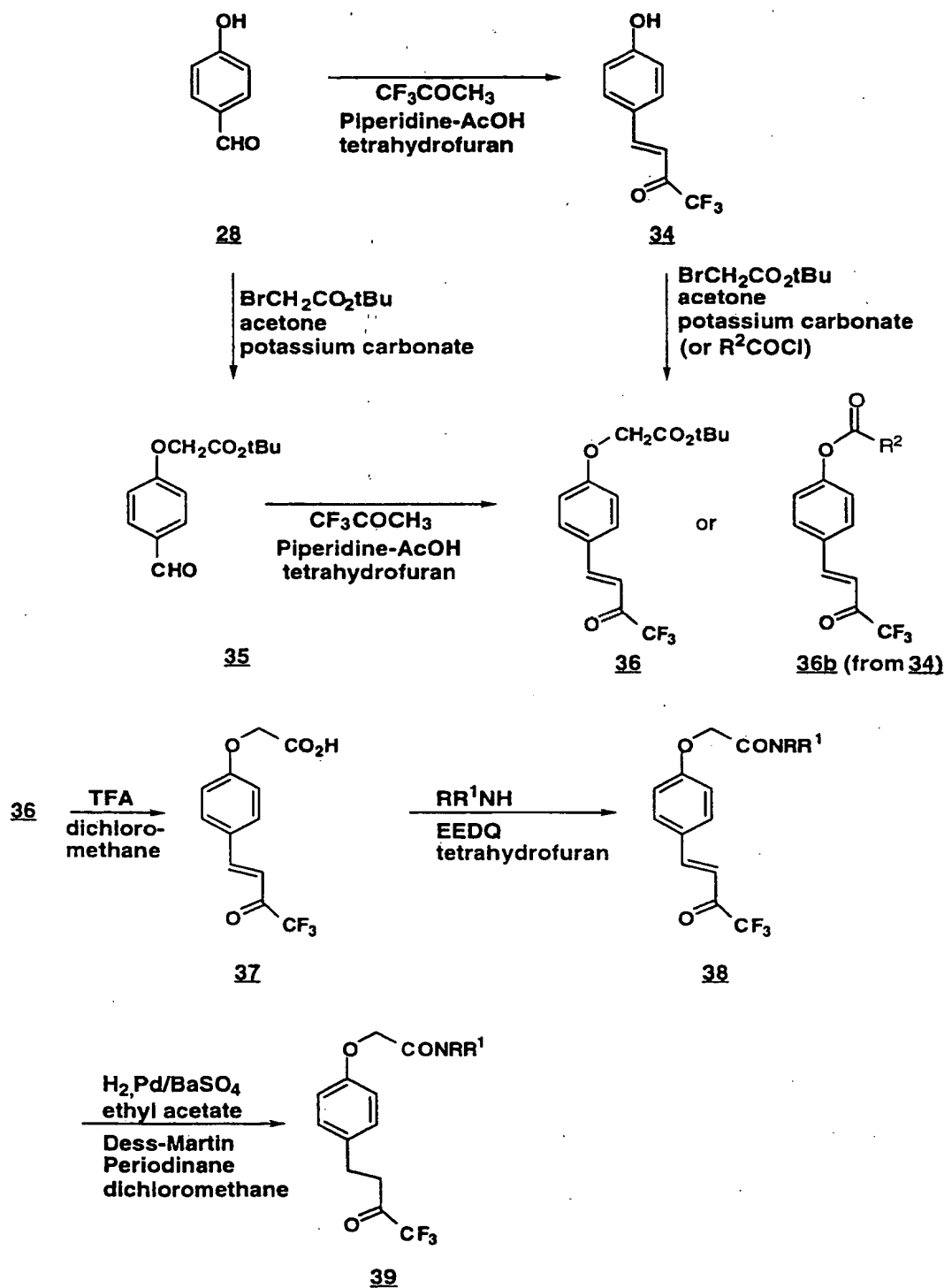


Exp. #	R ¹	R ²	Analysis
129	(CH ₂) ₁₁ CH ₃	COCF ₃	C ₂₆ H ₃₇ F ₆ NO ₃ . 0.4 H ₂ O Calcd: C 58.61, H 7.15, N 2.63 Found: C 58.48, H 6.98, N 2.73
130	(CH ₂) ₁₁ CH ₃	COC ₆ H ₅	C ₃₁ H ₄₂ F ₃ NO ₃ .0.4 H ₂ O Calcd: C 68.84, H 7.98, N 2.59 Found: C 68.61, H 8.05, N 2.59
131	(CH ₂) ₁₁ CH ₃	COCH ₂ CH ₂ CO ₂ Et	C ₃₀ H ₄₆ F ₃ NO ₅ . 0.4 H ₂ O Calcd: C 63.79, H 8.35, N 2.48 Found: C 63.5, H 8.38, N 2.49
132	(CH ₂) ₁₁ CH ₃	PO(OEt) ₂	C ₂₈ H ₄₇ F ₃ NO ₅ P. 0.4 H ₂ O Calcd: C 58.71, H 8.41, N 2.45 Found: C 58.43, H 8.59, N 2.52

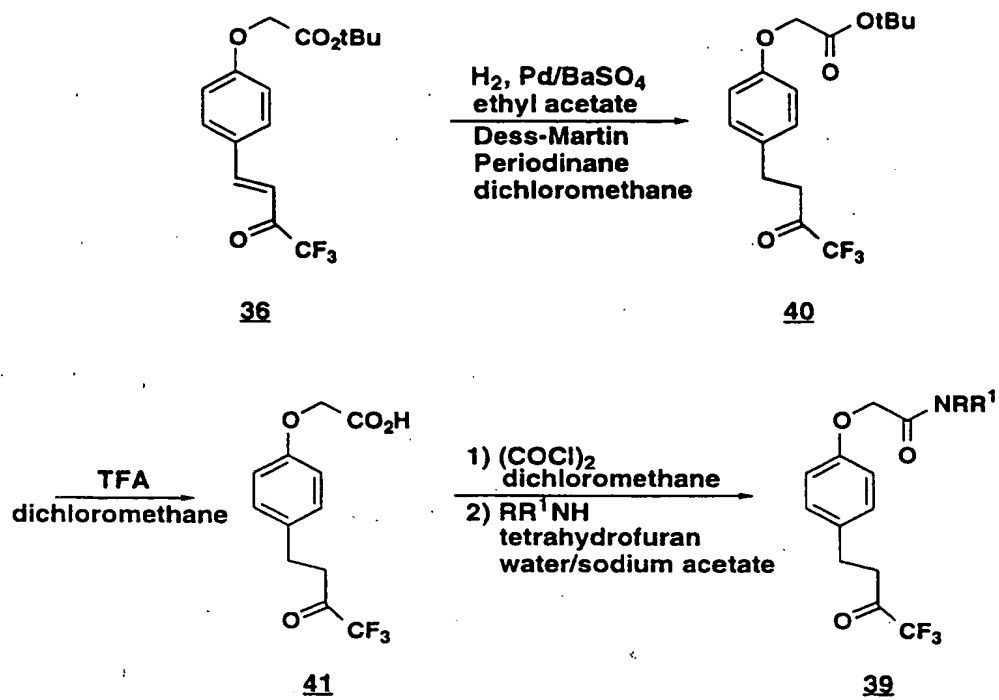
5

10

150

Scheme 8

151



Example 133**N-Dodecyl-4-(4,4,4-trifluoro-3-oxo-1-butyl)phenoxyacetamide**5 **(E)-1,1,1-trifluoro-4-(4-hydroxyphenyl)-3-buten-2-one**

A solution of 4-hydroxybenzaldehyde (5.0 g, 40.9 mmol) in tetrahydrofuran (165 ml) was treated with acetic acid (3.5 ml) and piperidine (3.5 ml). Then 1,1,1-trifluoroacetone (8 ml) was added dropwise. After 2 h at 22°C, another portion of 1,1,1-trifluoroacetone (8 ml) was added and the mixture was stirred for another 3 h. The reaction mixture was then diluted with ethyl acetate, washed with water, saturated ammonium chloride, saturated sodium bicarbonate, and brine. The organic phase was dried (magnesium sulfate), concentrated under reduced pressure and chromatographed on silica gel. Elution with a gradient of ethyl acetate (0 - 5%) in toluene gave 4.16 g (47%) of title material as yellow needles after crystallization from ether-hexane: mp 106-107°C.

Anal. Calcd. for C₁₀H₇F₃O₂: C 55.57, H 3.26.

20 Found: C 55.30, H 3.27.

(E)-4-(4,4,4-trifluoro-3-oxo-1-butenyl)phenoxyacetic acid, 1,1-dimethylethyl ester

25 A solution of (E)-1,1,1-trifluoro-4-(4-hydroxyphenyl) 3-buten-2-one (0.105 g, 0.49 mmol) in acetone (6 ml) was treated with powdered potassium carbonate (0.3 g) and tert-butyl bromoacetate (0.20 g, 1.02 mmol) and stirred at 22°C for 3 h. The reaction mixture was then diluted with toluene, washed with brine, dried (magnesium sulfate) and concentrated under reduced pressure. The residue was chromatographed on silica gel (elution toluene-ethyl acetate 2%) and gave 0.150 g (94%) of the title material as yellow needles: mp 112-113°C.

Anal. Calcd. for C₁₆H₁₇F₃O₄: C 58.18, H 5.19.

Found: C 58.12, H 5.18.

(E)-4-(4,4,4-trifluoro-3-oxo-1-butenyl)phenoxyacetic acid

- A solution of (E)-4-(4,4,4-trifluoro-3-oxo-1-butenyl)phenoxyacetic acid, 1,1-dimethylethyl ester (1.578 g, 4.77 mmol) in dichloromethane (90 ml) was
5 treated with trifluoroacetic acid (10 ml) and stirred at 22°C for 4 h. The solvent and excess reagent were evaporated under reduced pressure and the last traces of trifluoroacetic acid were co-evaporated with toluene. Crystallization of the residue from ethyl acetate-hexane gave 1.29 g (98%) of the title material as white cubes: mp 156-156.5°C.
- 10 Anal. Calcd. for C₁₂H₉F₃O₄: C 52.57, H 3.31.
Found: C 52.66, H 3.29.

(E)-N-dodecyl-4-(4,4,4-trifluoro-3-oxo-1-butenyl)phenoxyacetamide

- 15 A solution of (E)-4-(4,4,4-trifluoro-3-oxo-1-butenyl)phenoxyacetic acid (0.810 g, 2.95 mmol) in tetrahydrofuran (20 ml) was treated with EEDQ (0.767 g, 3.10 mmol) and dodecylamine (0.575 g, 3.10 mmol). After 2 h at 22°C, the reaction mixture was diluted with ethyl acetate, washed with water, 0.1N hydrochloric acid, saturated sodium bicarbonate, brine and
20 dried. Evaporation of the solvent under reduced pressure gave a solid which was chromatographed on silica gel. Elution with a mixture of toluene and ethyl acetate (8:12) gave 0.750 g (58%) of the title material as white needles after recrystallization from ethyl acetate-hexane: mp 78.5-79°C.
- 25 Anal. Calcd. for C₂₄H₃₄F₃NO₃: C 65.29, H 7.76, N 3.17.
Found: C 65.30, H 7.73, N 3.13.

N-dodecyl-4-(4,4,4-trifluoro-3-oxo-1-butyl)phenoxyacetamide

- 30 (E)-N-dodecyl-4-(4,4,4-trifluoro-3-oxo-1-butenyl)phenoxyacetamide (0.530 g, 1.20 mmol) was hydrogenated and re-oxidized as described in example 119 to give 0.490 g (92%) of the title material as an amorphous solid.
- Anal. Calcd. for C₂₄H₃₆F₃NO₃H₂O: C 62.45, H 8.30, N 3.03.
Found: C 62.54, H 8.19, N 3.18.

154

Example 134**N-[Bis-(4-chlorophenyl)methyl]-4-(4,4,4-trifluoro-3-oxo-1-butyl)-
phenoxyacetamide**

5

**4-(4,4,4-trifluoro-3-oxo-1-butyl)-phenoxyacetacetic acid, 1,1-dimethylethyl
ester**

10 E-(4,4,4-trifluoro-3-oxo-1-butenyl)-phenoxyacetacetic acid, 1,1-dimethylethyl ester (1.95 g, 5.90 mmol) was hydrogenated and re-oxidized as described in example 133 to give 1.93 g (98%) of the title material as a wax.

Anal. Calcd. for C₁₆H₁₉F₃O₄: C 55.43, H 5.99.

Found: C 55.32, H 5.90.

15

4-(4,4,4-trifluoro-3-oxo-1-butyl)phenoxyacetic acid

20 4-(4,4,4-trifluoro-3-oxo-1-butyl)phenoxyacetic acid 1,1-dimethylethyl ester (0.450 g, 1.35 mmol) was treated with trifluoroacetic acid as described in example (133) to give 0.373 g (100%) of the material as a white solid.

N-[Bis-(4-chlorophenyl)methyl]-4-(4,4,4-trifluoro-3-oxo-1-butyl)phenoxyacetamide

25 A solution of 4-(4,4,4-trifluoro-3-oxo-1-butyl)phenoxyacetic acid (0.374 g, 1.35 mmol) in dichloromethane (10 ml) was treated with oxalyl chloride (0.17 ml, 2.03 mmol) and a trace of N,N-dimethylformamide. After 30 min at 22°C, the solvent and excess reagent were evaporated under reduced pressure and the residual oil obtained was dissolved in
30 anhydrous tetrahydrofuran (10 ml). This solution was then added dropwise to a vigorously stirred solution of p-chlorobenzhydrylamine hydrochloride (0.39 g, 1.35 mmol) in a mixture of tetrahydrofuran (10 ml) and 40% aqueous sodium acetate (10 ml). After 30 min at 22°C, the

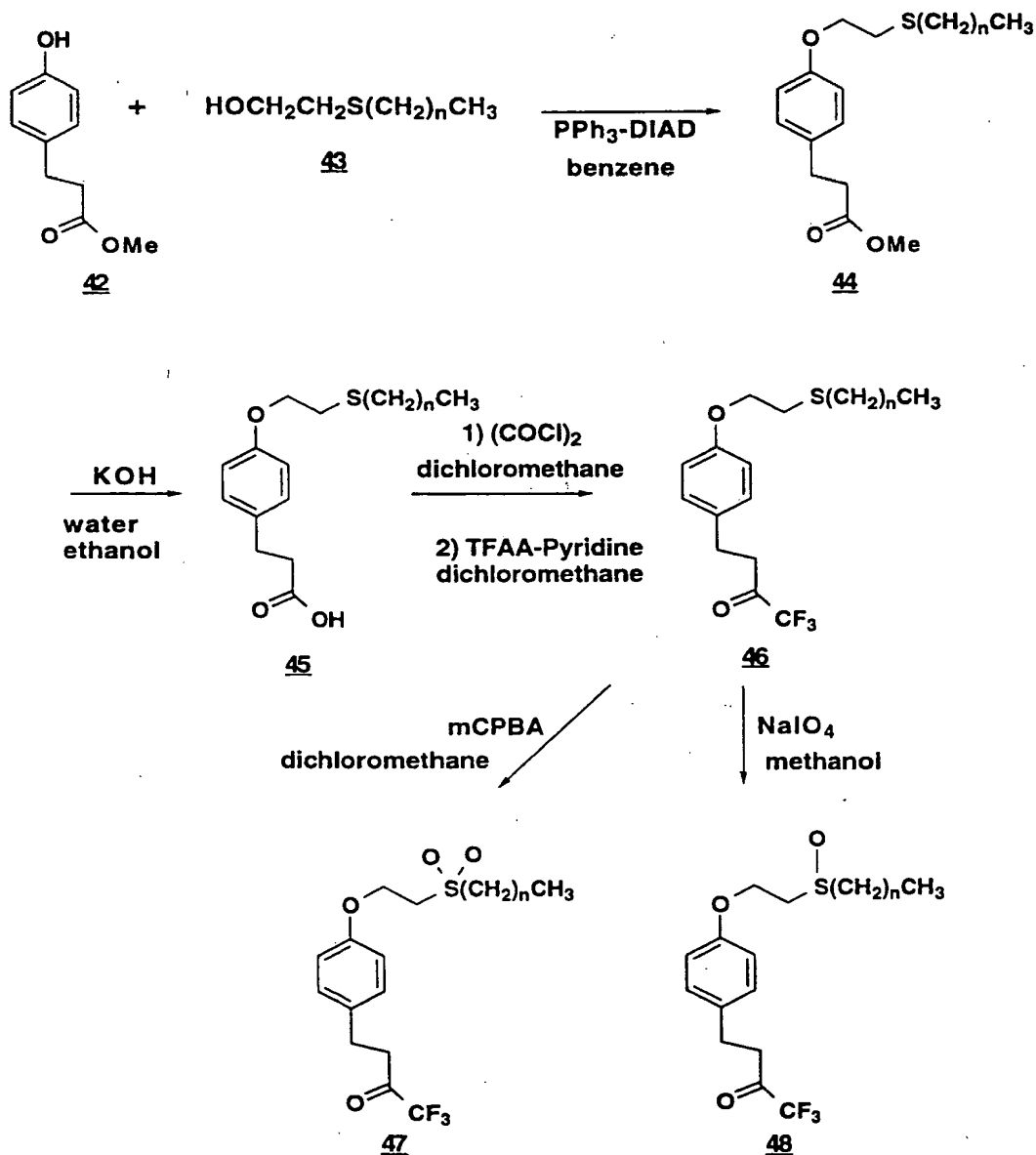
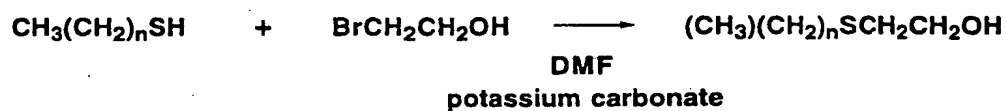
155

reaction mixture was diluted with ethyl acetate, washed with water, brine and dried. Evaporation of the solvent under reduced pressure gave a solid which was chromatographed on silica gel. Elution with a mixture of toluene and ethyl acetate (8:2) gave 0.603 g (87%) of the title product as
5 white crystals: mp 145-146°C.

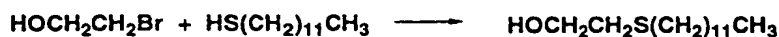
Anal. Calcd. for $C_{25}H_{20}ClF_3NO_3$: C 58.84, H 3.85, N 2.74, Cl 13.89, F 11.17.

Found: C 58.73, H 4.07, N 2.82, Cl 13.60, F 10.46.

156

Scheme 9

157

Example 1354-[4-[2-(Dodecylthio)ethoxyphenyl]-1,1,1-trifluoro-2-butanone5 2-(Dodecylthio) Ethanol

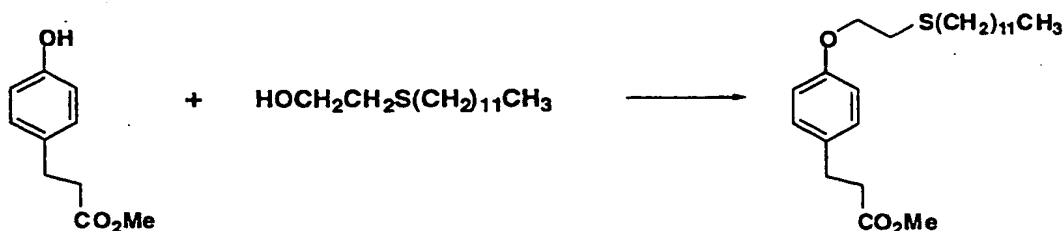
A mixture of 2-bromoethanol (6.08 g, 48.7 mmol), dodecanethiol (9.86 g, 48.7 mmol) and potassium carbonate (11 g) in dry N,N-dimethylformamide (100 ml) was stirred at 22°C for 10 h. The reaction mixture was then diluted with toluene (400 ml) washed with water and dried (magnesium sulfate). The solvent was evaporated under reduced pressure and the residue was filtered through a silica gel pad (toluene - ethyl acetate 95:5) and distilled under vacuum to give 9.18 g (77%) of 2-(dodecylthio)ethanol as a clear oil which solidified on standing: b.p. 100-105°C/0,01 torr (bulb to bulb distillation, air bath temperature); m.p. 31-32°C.

IR (NaCl, film) μ_{max} (cm⁻¹) : 3380 (OH).
 20 ¹H NMR 400 MHz (CDCl₃) d (ppm) : 0.89 (3H, t, J=6.8 Hz, CH₃), 1.2-1.7 (20H, m, (CH₂)₁₀), 2.16 (1H, br t, OH), 2.52 (2H, t, J=7.4 Hz, SCH₂), 2.74 (2H, t, J=6.0 Hz, OCH₂CH₂S), 3.7 (2H, q, J=6.0 Hz, OCH₂CH₂S).

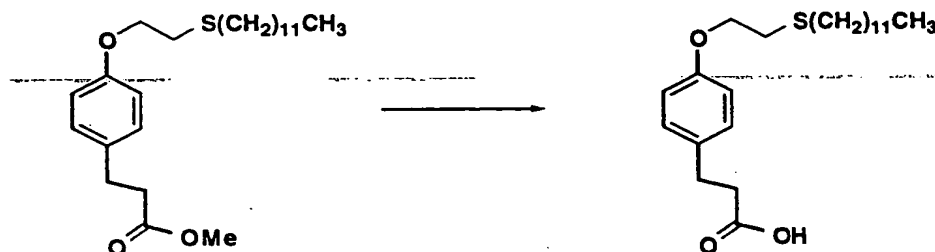
Anal. Calcd. for C₁₄H₃₀OS: C 68.23, H 12.27, N 13.01.

Found: C 68.06, H 12.29, N 12.95.

158

3-[4-[2-(Dodecylthio)ethoxy]phenyl]propanoic acid methyl ester

- 5 A solution of methyl 3-[4-hydroxyphenyl]propionate (2.46 g, 13.6 mmol), 2-(dodecylthio)ethanol (3.40 g, 13.7 mmol) and triphenylphosphine (3.60 g, 13.8 mmol) in dry benzene (50 ml) was treated at 22°C with diethyl azodicarboxylate (2.43 g, 13.9 mmol) added dropwise over 10 min. After 3 h at 22°C, the reaction mixture was diluted with ethyl acetate, washed
- 10 with water, brine and dried (magnesium sulfate). Evaporation under reduced pressure gave an oil which was triturated with hexane to precipitate the triphenylphosphine oxide and the hydrazine side products. The filtrate was chromatographed on silica gel using a gradient of ethyl acetate (0-5%) in hexane as eluent to give 4.70 g(84%) of 3-[4-[2-
- 15 (dodecylthio)ethoxy]phenyl]propanoic acid methyl ester as a white solid. Recrystallization from methanol gives white leaflets : m.p. 48°C. IR (KBr) μ_{\max} (cm⁻¹) : 1729 (C=O of ester). ¹H NMR 400 MHz (CDCl₃) d (ppm) : 0.89 (3H, t, J=6.8 Hz, CH₃), 1.2-1.7 (20H, m, (CH₂)₁₀), 2.6 (4H, br t, SCH₂ and CH₂CO), 2.9 (4H, br t, OCH₂CH₂S and PhCH₂), 3.68 (3H, s, OCH₃), 4.11 (2H, t, J=7.03 Hz, OCH₂CH₂S), 6.83 (2H, d, J=8.7 Hz aromatic), 7.12 (2H, d, J=8.7 Hz, aromatic).
- 20 Anal. Calc. for C₂₄H₄₀O₃S: C 70.54, H 9.87, S 7.85. Found: C 70.25, H 9.38, S 7.87.

3-[4-[2-(Dodecylthio)ethoxy]phenyl]propanoic acid

- 5 A suspension of 2-[4-[2-(dodecylthio)ethoxy]phenyl]propanoic acid methyl ester (4.70 g, 11.5 mmol) in 80% ethanol (100 ml) was treated with a solution of potassium hydroxide (1.33 g, 20.1 mmol) in water (10 ml) and the mixture was stirred at 55°C for 1 h. The solvent was then concentrated *in vacuo* and the residue was diluted with water (100 ml) and
- 10 dichloromethane (250 ml). The solution was then adjusted to pH 2 with diluted hydrochloric acid and the aqueous phase was extracted a second time with dichloromethane. The combined organic extracts were washed with brine and dried (magnesium sulfate). Evaporation of the solvent under reduced pressure and crystallization of the residue from ethyl
- 15 acetate-hexane gave 3.56 g (78%) of 3-[4-[2-(dodecylthio)ethoxy]phenyl]propanoic acid as white prisms: m.p. 68-69°C. IR (NaCl, film) μ_{\max} (cm⁻¹) : 1710 (C=O). ¹H NMR 400 MHz (CDCl₃) δ (ppm) : 0.89 (3H, t, J=6.8 Hz, -CH₃), 1.1-1.7 (20H, m, (CH₂)₁₀), 2.63 (4H, m, SCH₂ and CH₂CO), 2.90, (4H, m, OCH₂CH₂S and PhCH₂), 4.12 (2H, t, J=6.99, OCH₂CH₂S), 6.84 (2H, d, J=8.5 Hz, aromatic), 7.13 (2H, d, J=8.5 Hz, aromatic).
- 20 Anal. calcd. for C₂₃H₃₈O₃S . 0.1 H₂O: C 69.69, H 9.71, S 8.09. Found: C 69.55, H 9.86, S 8.15.

160

4-[4-[2-(Dodecylthio)ethoxy]phenyl]-1,1,1-trifluoro-2-butanone

- 5 A solution of 3-[4-[2-(dodecylthio)ethoxy]phenyl]propanoic acid (14.13 g, 35.8 mmol) in dichloromethane (400 ml) was treated with oxalyl chloride (6.5 ml) and a drop of N,N-dimethylformamide and the resulting mixture was stirred at 22°C for 1 h. The solvent and excess reagent were
- 10 evaporated under reduced pressure and the residue was dissolved in dry dichloromethane (200 ml). This solution was added to a cold (0°C) solution of trifluoroacetic anhydride (19.2 ml, 0.107 mol) in dichloromethane (200 ml). Then pyridine (6.1 ml, 75.4 mmol) was added dropwise and the resulting solution was stirred at 0°C for 30 min and then at 22°C for 2 h. Water (50 ml) was added and the mixture was stirred for
- 15 another 30 min. The organic phase was then washed with brine, dried and concentrated under reduced pressure. Chromatography on silica gel (elution with a gradient of ethyl acetate 0-10% in toluene) gave 10.50 g (66%) of 4-[4-[2-(dodecylthio)ethoxy]phenyl]-1,1,1-trifluoro-2-butanone as an amorphous solid.
- 20 IR (NaCl, film) μ_{\max} (cm⁻¹) : 1758 (C=O).
¹H NMR 400 MHz (CDCl₃) d (ppm) : 0.89 (3H, t, J=6.8 Hz, -CH₃), 1.2-1.7 (20H, m, (CH₂)₁₀), 2.62 (2H, t, J=7.46 Hz, SCH₂), 2.89 (2H, t, J=6.95 Hz, OCH₂CH₂S), 2.9-3.1 (4H, m, CH₂CH₂CO), 4.12 (2H, t, J=6.95 Hz, OCH₂CH₂S), 6.85 (2H, d, J=8.7 Hz, aromatic), 7.11 (2H, d, J=8.7 Hz,
- 25 aromatic).

16

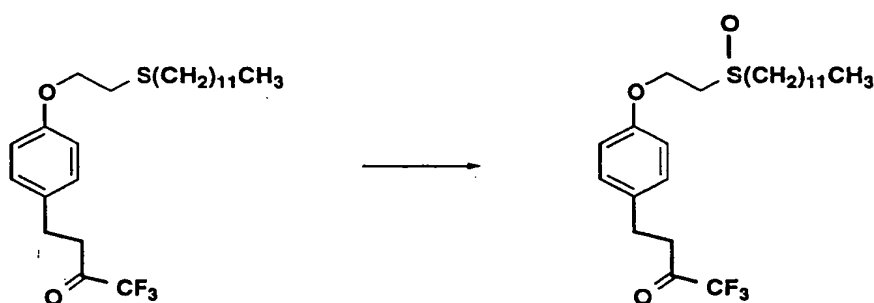
Anal. Calcd. for $C_{24}H_{37}F_3O_2S$: C 64.54, H 8.35.

Found: C 64.47, H 8.32.

Example 136

5

4-[4-[2-(Dodecylsulfinyl)ethoxy]phenyl]-1,1,1-trifluoro-2-butanone



- 10 A solution of 4-[4-[2-(dodecylthio)ethoxy]phenyl]-1,1,1-trifluoro-2-butanone (0.340 g, 0.76 mmol) in methanol (15 ml) was treated with a solution of sodium periodate (0.165 g, 0.77 mmol) in water (3 ml) and the resulting mixture was stirred at 22°C for 18 h. The solid formed was filtered and washed with methanol. This filtrate was then concentrated
- 15 under reduced pressure and then partitioned between water and ethyl acetate. The organic phase was then dried (magnesium sulfate) and concentrated. The residue was chromatographed on silica gel (elution toluene-ethyl acetate 1:1) to give 0.335 g (90%) of 4-[4-[2-(dodecylsulfinyl)ethoxy]phenyl]-1,1,1-trifluoro-2-butanone as a white
- 20 solid. By ^1H NMR this product was a 6:4 mixture of trifluoromethyl ketone and hydrated trifluoromethyl ketone. The pure hydrate precipitates from ethyl acetate-hexane: m.p. 98-100°C.
- IR (NaCl, film) μ_{max} (cm^{-1}) : 3400 (OH), 1650.

162

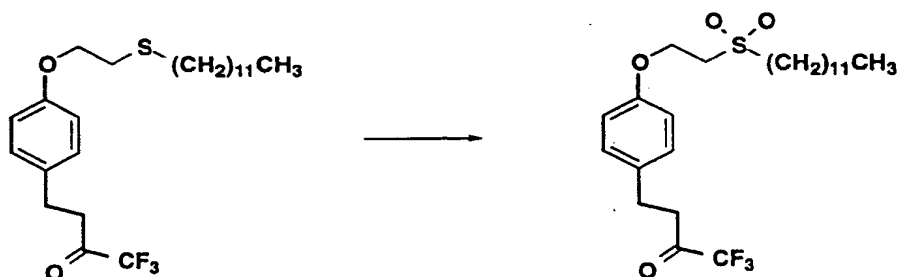
^1H NMR 400 MHz (CDCl_3) δ (ppm) : 0.89 (3H, t, $J=6.8$ Hz, $-\text{CH}_3$), 1.3, 1.45 and 1.8 (16H, 2H and 2N, 3m, $(\text{CH}_2)_{10}$), 2.09 (2H, br t, $J=8$ Hz, $\text{CH}_2\text{CH}_2\text{CO}$), 3.7 (2H, br, OH), 4.4 (2H, m, OCH_2), 6.84 (2H, d, $J=8.5$ Hz, aromatic), 7.15 (2H, d, $J=8.5$ Hz, aromatic).

5 Anal. Calcd. for $\text{C}_{24}\text{H}_{37}\text{F}_3\text{S}\cdot\text{H}_2\text{O}$: C 59.98, H 8.18, S 6.67.

Found: C 60.06, H 8.17, S 6.67.

Example 137

10 4-[4-[2-(Dodecylsulfonyl)ethoxy]phenyl]-1,1,1-trifluoro-2-butanone



A solution of 4-[4-[2-(dodecylthio)ethoxy]phenyl]-1,1,1-trifluoro-2-butanone (0.394 g, 0.88 mmol) in dichloromethane (25 ml) was treated at 22°C with 85% m-chloroperbenzoic acid (0.40 g, 1.8 mmol) and the resulting mixture was stirred for 2.5 h. The reaction mixture was then washed with aqueous sodium bicarbonate, brine and dried (magnesium sulfate). Evaporation and chromatography on silica gel (elution with a gradient of ethyl acetate 0-20% in toluene) gave 0.344 g (82%) of 4-[4-[2-(dodecylsulfonyl)ethoxy]phenyl]-1,1,1-trifluorobutanone as an amorphous solid. By ^1H NMR, this product is a ~1:1 mixture of trifluoromethylketone and hydrated trifluoromethyl ketone: m.p. 55-56°C.

IR (NaCl, film) ν_{max} (cm^{-1}) : 3400 (OH) and 1760 ($\text{C}=\text{O}$).

163

^1H NMR 400 MHz (CDCl_3).

Ketone form : d (ppm) : 0.89 (3H, t, $J=6.8$ Hz, $-\text{CH}_3$), 1.28, 1.45 and 1.9 (16H, 2H and 2H, 3 m, $(\text{CH}_2)_{10}$), 3.0 (4H, m, $\text{CH}_2\text{CH}_2\text{CO}$), 3.12 (2H, m, SO_2CH_2),
 5 3.4 (2H, t, $J=5.35$ Hz, $\text{OCH}_2\text{CH}_2\text{S}$), 4.41 (2H, t, $J=5.35$ Hz, $\text{OCH}_2\text{CH}_2\text{S}$), 6.84 (2H, d, $J=8.6$ Hz, aromatic), 7.15 (2H, d, $J=8.6$ Hz, aromatic).

Hydrate form : d (ppm) : 2.14 (2H, br t, $J=8.1$ Hz, $\text{CH}_2\text{CH}_2\text{CO}$), 2.87 (2H, br t, $J=8.1$ Hz, $\text{CH}_2\text{CH}_2\text{CO}$), 6.86 (2H, d, $J=8.6$ Hz, aromatic), 7.2 (2H, d, $J=8.6$ Hz, aromatic).
 10

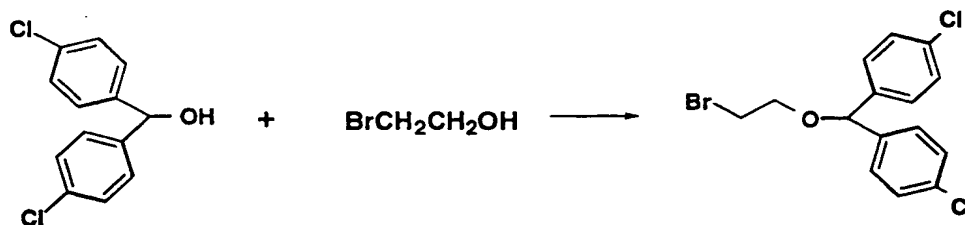
Anal. Calcd. for $\text{C}_{24}\text{H}_{37}\text{F}_3\text{O}_4\text{S} \cdot 0.6 \text{ H}_2\text{O}$: C 58.90, H 7.87, S 6.55.

Found: C 58.86, H 7.79, S 6.63.

15 Example 138

4-[4-[2-[2-[Bis(4-chlorophenyl)methoxy]ethylsulfonyl]ethoxy]phenyl]-1,1,1-trifluoro-2-butanone

20 2-[Bis(4-chlorophenyl)methoxy]ethyl bromide.

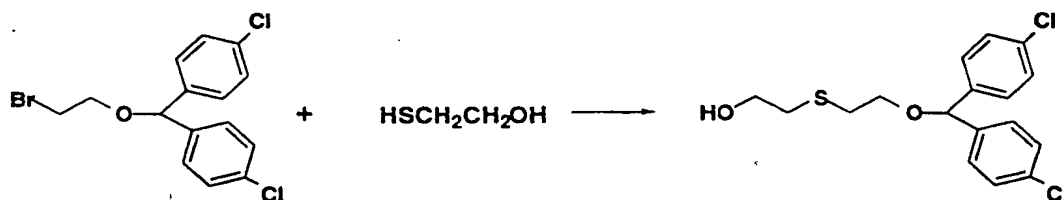


A mixture of 4,4'-dichlorobenzhydrol (4.40 g, 0.17 mmol) and 2-bromoethanol (3.0 g, 24.0 mmol) in benzene (50 ml) was treated with
 25 sulfuric acid (0.25 ml) and the resulting mixture was heated under reflux

164

for 1 h. The cooled mixture was diluted with ethyl acetate (200 ml), washed with saturated sodium bicarbonate, brine and dried over magnesium sulfate. Evaporation of the solvent gave an oil which was chromatographed on silica gel using a mixture of toluene and hexane (1:1) as eluent to give the title compound as a clear oil (5.13 g, 82%).

2-[2-[Bis(4-chlorophenyl)methoxy]ethylthio]ethanol



10

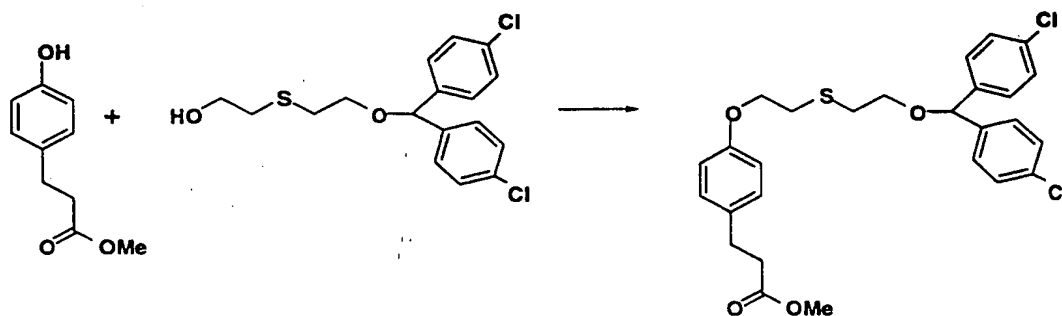
A solution of 2-[bis(4-chlorophenyl)methoxy]ethyl bromide (5.13 g, 14.2 mmol) in N,N-dimethylformamide (50 ml) was treated at 22°C with powdered anhydrous potassium carbonate (3.0 g, 21.7 mmol) followed by 2-mercaptoethanol (1.25 g, 16.0 mmol). The resulting mixture was stirred at 22° for 18 h. The reaction mixture was then diluted with toluene (400 ml) washed with water, brine and dried over magnesium sulfate. Evaporation of the solvent gave an oil which was chromatographed on silica gel (elution ethyl acetate 0-10% in toluene) to give 4.93 g (96%) of the title material as a clear oil.

Anal. Calcd. for $\text{C}_{17}\text{H}_{18}\text{Cl}_2\text{O}_2\text{S}$: C 57.15, H 5.08, S 8.97. Found: C 56.99, H 4.82, S 9.05.

25

165

3-[4-[2-[2-[Bis(4-chlorophenyl)methoxy]ethylthio]ethoxy]phenyl]propionic acid methyl ester



5

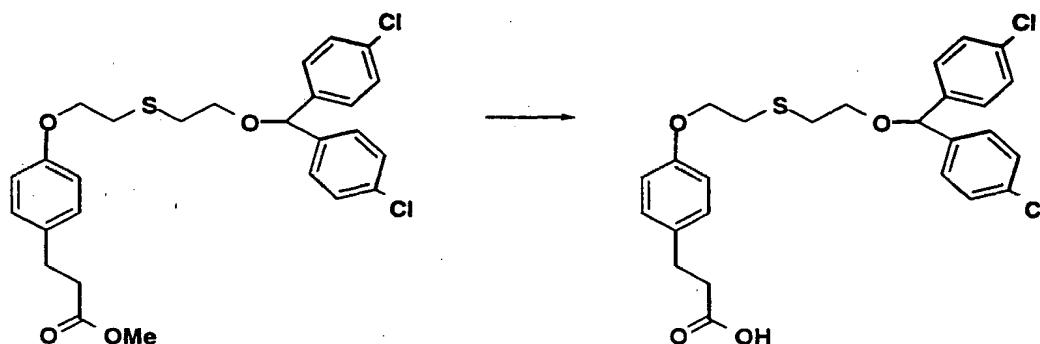
A solution of methyl 3-(4-hydroxyphenyl) propionate (1.40 g, 7.77 mmol), 2-[2-[bis(4-chlorophenyl)methoxy]ethylthio]ethanol (2.80 g, 7.80 mmol) and triphenylphosphine (2.0 g, 7.8 mmol) in dry benzene (30 ml) was treated at 22°C with diethyl azodicarboxylate (1.34 g, 7.8) added dropwise over 5 min. After 18 h at 22°C, the reaction mixture was diluted with ethyl acetate (200 ml) washed with saturated sodium bicarbonate and dried over magnesium sulfate. Evaporation of the solvent gave an oil which was triturated in a mixture of hexane and toluene (6:4) to crystallize the triphenylphosphine oxide and the hydrazine side products. The filtrate was chromatographed on silica gel (elution ethyl acetate 0-5% in toluene) to give 2.90 g (71%) of the title material as an oil.

Anal. Calcd. for C₂₇H₂₈Cl₂O₄S: C 62.43, H 5.43, S 6.17. Found: C 61.89, H 5.21, S 6.11.

20

166

3-[4-[2-[2-[Bis(4-chlorophenyl)methoxy]ethylthio]ethoxy]phenyl]propionic acid



5

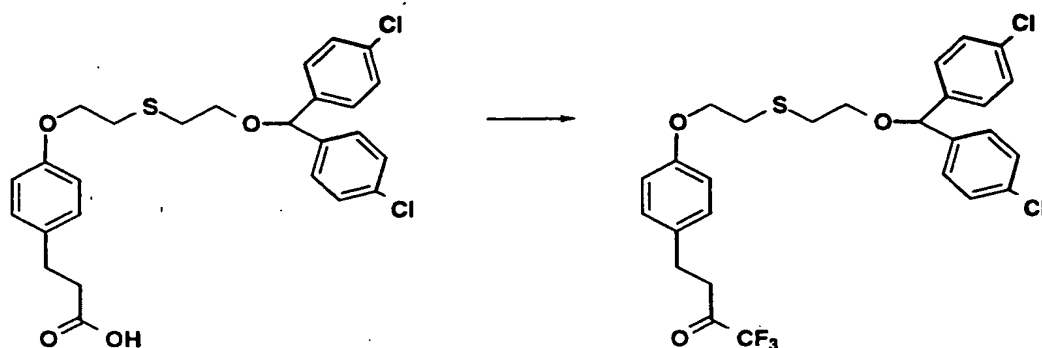
A mixture of 3-[4-[2-[2-[Bis(4-chlorophenyl)methoxy]ethylthio]ethoxy]phenyl] propionic acid methyl ester (2.76 g, 5.31 mmol) and 80% aqueous ethanol (50 ml) was treated with a solution of potassium hydroxide (0.7 g, 10.6 mmol) in water (3 ml) and the resulting mixture was heated at 60°C for 1 h. The solvent was then concentrated *in vacuo* and the residue was diluted with water (30 ml) and dichloromethane (50 ml) and acidified to pH4 with 2N hydrochloric acid. The aqueous phase was extracted a second time with dichloromethane and the combined organic extracts were washed with brine and dried (magnesium sulfate). Evaporation of the solvent under reduced pressure gave 2.63 g (98%) of the title acid as a white solid.

Anal. Calcd. for C₂₆H₂₆Cl₂O₄S: C 61.78, H 5.18, S 6.34. Found: C 61.42, H 5.11, S 6.34.

20

167

4-[4-[2-[2-[Bis(4-chlorophenyl)methoxy]ethylthio]ethoxy]phenyl]-1,1,1-
trifluoro-2-butanone



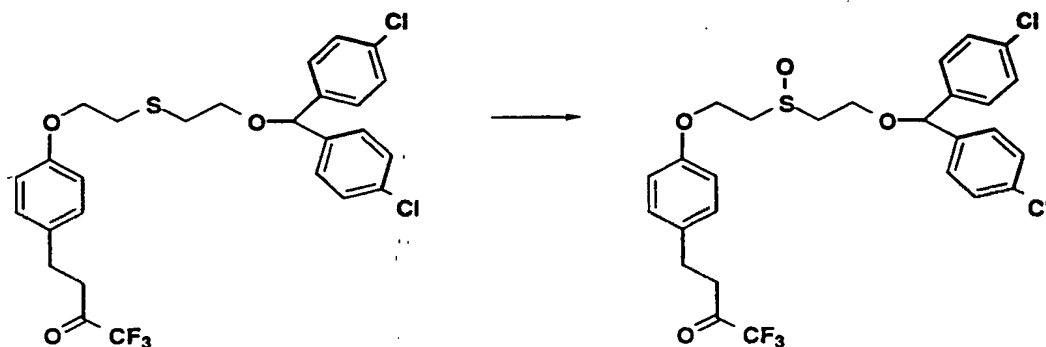
5

A solution of 3-[4-[2-[2-[bis(4-chlorophenyl)methoxy]ethylthio]ethoxy]phenyl]propionic acid (2.49 g, 4.93 mmol) in dry dichloromethane (25 ml) was treated at 22°C with oxalyl chloride (1.5 g, 11.8 mmol) and a small drop of N,N-dimethylformamide.

- 10 After 1 h, the solvent and excess reagent were evaporated *in vacuo* and the residue was diluted with dry toluene (75 ml). The solution was then cooled to 0-5°C, treated with trifluoroacetic anhydride (3.12 g, 14.9 mmol) followed by pyridine (0.98 g, 12.4 mmol) added dropwise over 10 min. The reaction mixture was then allowed to warm up to 20°C and stirred for
- 15 another 2 h. Then water (5 ml) was added dropwise and the mixture was stirred for another 15 min. The reaction mixture was then diluted with ethyl acetate (300 ml) washed with water, saturated sodium bicarbonate, brine and dried (magnesium sulfate). Evaporation gave an oil which was chromatographed on silica gel. Elution with a gradient of ethyl acetate (0-
- 20 4%) in toluene gave 2.35 g (85%) of the title material as an oil.
- Anal. Calcd. for C₂₇H₂₅Cl₂F₃O₃S.0.4 H₂O: C 57.43, H 4.63, S 5.68. Found: C 57.42, H 4.41, S 5.49.

168

4-[4-[2-[2-[Bis(4-chlorophenyl)methoxy]ethylsulfinyl]ethoxy]phenyl]-1,1,1-trifluoro-2-butanone



5

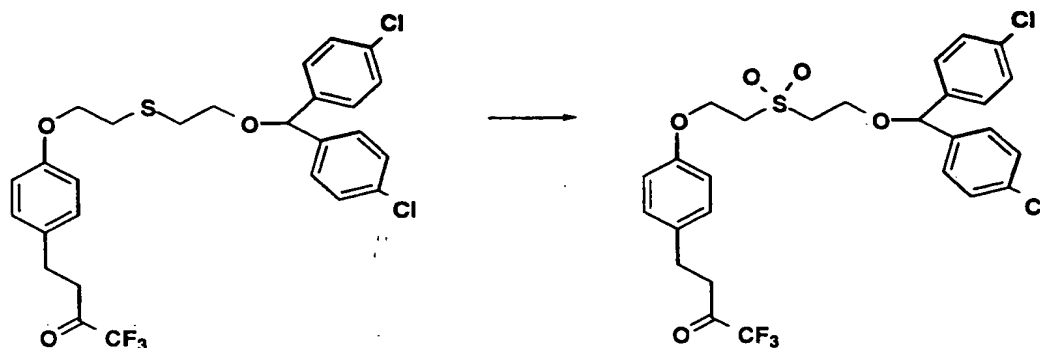
A solution of 4-[4-[2-[2-[bis(4-chlorophenyl)methoxy]ethylthio]ethoxy]phenyl]-1,1,1-trifluoro-2-butanone (0.88 g, 1.58 mmol) in methanol (40 ml) was treated at 22°C with a solution of sodium periodate (0.34 g, 1.58 mmol) in water (2 ml). After 6.5 h the solid formed was filtered and the filtrate was evaporated *in vacuo*. The residue was diluted with ethyl acetate, washed successively with sodium bicarbonate, water and brine, dried (magnesium sulfate) and concentrated. The residue was chromatographed on silica gel (elution ethyl acetate) to give 0.691 g (76%) of the title material as an oil.

Anal. Calcd. for C₂₇H₂₅Cl₂F₃O₄S. 0.6 H₂O: C 55.51, H 4.52, S 5.49. Found: C 55.37, H 4.31, S 5.39.

20

169

4-[4-[2-[2-[Bis(4-chlorophenyl)methoxy]ethylsulfonyl]ethoxy]phenyl]-1,1,1-trifluoro-2-butanone



5

- A solution of 4-[4-[2-[2-[bis(4-chlorophenyl)methoxy]ethylthio]ethoxy]phenyl]-1,1,1-trifluoro-2-butanone (1.51 g, 2.71 mmol) in dichloromethane (50 ml) was treated at 22°C with m-chloroperbenzoic acid (0.94 g, 5.4 mmol) and the resulting mixture was stirred for 2 h. The reaction mixture was then diluted with ethyl acetate, washed with sodium bicarbonate, brine and dried (magnesium sulfate). Evaporation and chromatography on silica gel (elution toluene-ethyl acetate 8:2) gave 1.46 g (92%) of the title material as an oil which crystallized upon standing: mp 98-100°C.
- IR (NaCl, film) ν_{max} (cm^{-1}) 1755.
- ^1H NMR 400 MHz (CDCl_3) δ (ppm): 2.97 (2H, m), 3.02 (2H, m), 3.45 (2H, t, $J=5.6$ Hz), 3.53 (2H, t, $J=5.6$ Hz), 3.92 (2H, t, $J=5.6$ Hz), 4.41 (2H, m), 5.39 (1H, s), 6.92 and 7.1-7.3 (12H, aromatic). Hydrated form: 2.15 and 2.87 (2m).
- Anal. Calcd. for $\text{C}_{27}\text{H}_{25}\text{Cl}_2\text{F}_3\text{O}_5\text{S}$: C 55.02, H 4.27, S 5.44. Found:
- C 54.83, H 4.36, S 5.54.

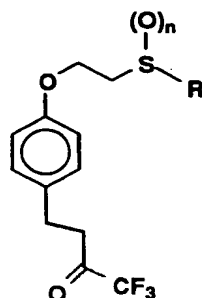
20

The following compounds may be prepared by the general procedure of Scheme 9.

25

170

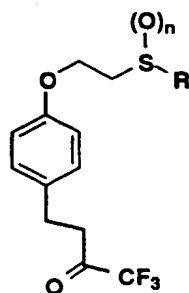
SCHEME 9



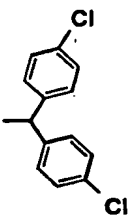
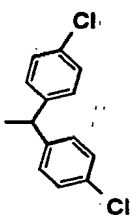
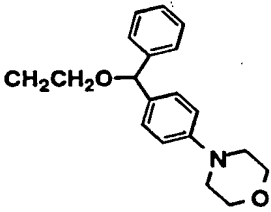
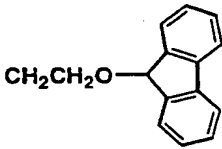
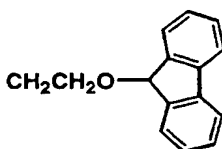
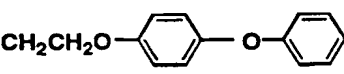
Exp. #	n	R	Analysis
139	0	(CH ₂) ₆ CH ₃	C ₁₉ H ₂₇ F ₃ O ₂ S Calcd: C 60.62, H 7.23, S 8.52 Found: C 60.65, H 7.06, N 8.25
140	1	(CH ₂) ₆ CH ₃	C ₁₉ H ₂₇ F ₃ O ₃ S Calcd: C 55.59, H 7.12, S 7.81 Found: C 55.55, H 6.94, S 7.72
141	2	(CH ₂) ₆ CH ₃	C ₁₉ H ₂₇ F ₃ O ₄ S Calcd: C 55.87, H 6.66, S 7.85 Found: C 55.61, H 6.30, S 7.80

171

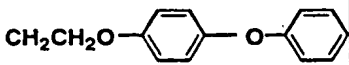
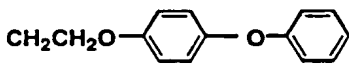
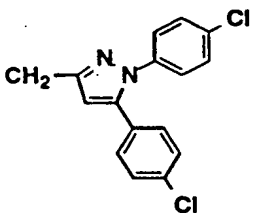
Scheme 9 (continued)



Exp. #	n	R	Analysis
142	0	$(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_3$	$\text{C}_{19}\text{H}_{27}\text{F}_3\text{O}_5\text{S} \cdot 0.7 \text{ H}_2\text{O}$ Calcd: C 52.21, H 6.55, S 7.34 Found: C 52.20, H 6.76, S 7.37
143	1	$(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_3$	$\text{C}_{19}\text{H}_{27}\text{F}_3\text{O}_6 \cdot 0.8 \text{ H}_2\text{O}$ Calcd: C 50.17, H 6.34, S 7.05 Found: C 50.11, H 6.25, S 7.08
144	2	$(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_3$	$\text{C}_{19}\text{H}_{27}\text{F}_3\text{O}_7\text{S} \cdot 0.7 \text{ H}_2\text{O}$ Calcd: C 48.65, H 6.10, S 6.84 Found: C 48.72, H 6.16, S 7.00
145	0		$\text{C}_{25}\text{H}_{21}\text{Cl}_2\text{F}_3\text{O}_2\text{S}$ Calcd: C 58.49, H 4.12, S 6.25 Found: C 58.43, H 4.06, S 6.39

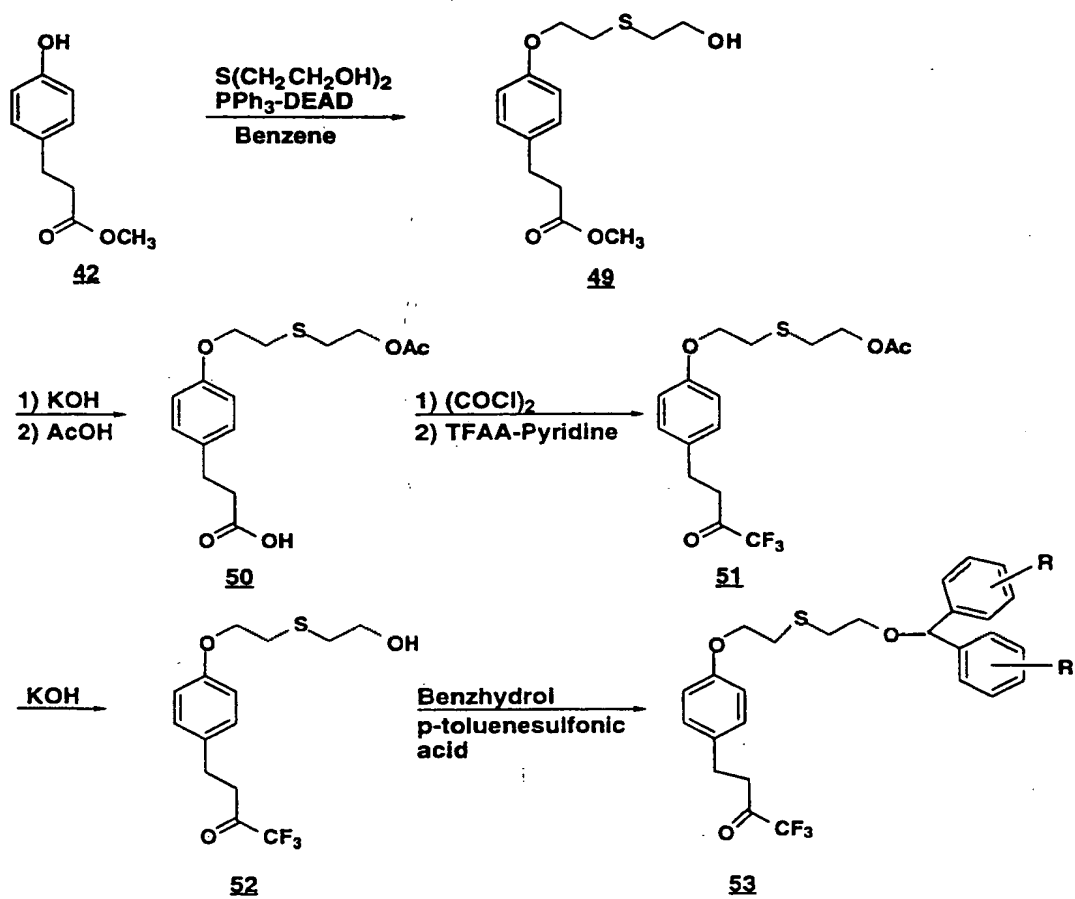
146	1		<p>$C_{25}H_{21}Cl_2F_3O_3S \cdot 1.5 H_2O$</p> <p>Calcd: C 53.96, H 4.35, S 5.76</p> <p>Found: C 53.92, H 4.08, S 5.90</p>
147	2		<p>$C_{25}H_{21}Cl_2F_3O_4S \cdot 0.3 H_2O$</p> <p>Calcd: C 54.52, H 3.95, S 5.82</p> <p>Found: C 54.52, H 3.79, S 5.91</p>
148	0		<p>$C_{31}H_{34}F_3NO_4S \cdot HCl \cdot 0.5 H_2O$</p> <p>Calcd: C 60.14, H 5.86, N 2.26</p> <p>Found: C 59.94, H 5.96, N 2.31</p>
149	0		<p>$C_{27}H_{25}F_3O_3S$</p> <p>Calcd: C 66.65, H 5.18</p> <p>Found: C 66.83, H 5.16</p>
150	2		<p>$C_{27}H_{25}F_3O_5S \cdot 1.1 H_2O$</p> <p>Calcd: C 60.24, H 5.09</p> <p>Found: C 59.96, H 4.73</p>
151	0		<p>$C_{26}H_{24}ClF_3O_4S$</p> <p>Calcd: C 59.48, H 4.61, S 6.11</p> <p>Found: C 59.21, S 4.45, S 6.16</p>

173

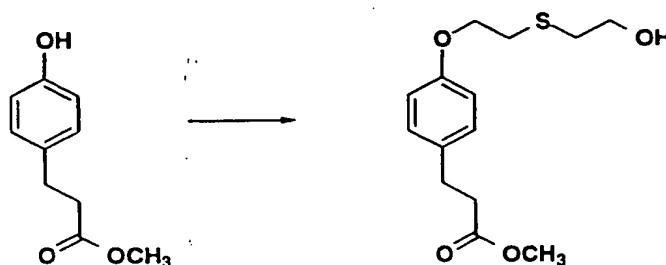
152	1		$C_{26}H_{24}ClF_3O_5S \cdot 0.8 H_2O$ Calcd: C 56.23, H 4.65, S 5.77 Found: C 56.13, S 4.62, S 5.96
153	2		$C_{26}H_{24}ClF_3O_6S \cdot 0.4 H_2O$ Calcd: C 55.35, H 4.43, S 5.68 Found: C 55.30, S 4.27, S 5.88
154	0	$CH_2CH_2OSi(CH_3)_2tBu$	$C_{20}H_{31}F_3O_6SSi \cdot 0.2 H_2O$ Calcd: C 54.57, H 7.19 Found: C 54.26, H 7.01
155	0	$CH_2CH_2OSi(Ph)_2tBu$	$C_{30}H_{35}F_3O_3SSi$ Calcd: C 64.26, H 6.29, S 5.72 Found: C 64.01, H 6.16, S 5.58
156	1	$CH_2CH_2OSi(Ph)_2tBu$	$C_{30}H_{35}F_3O_4SSi \cdot 0.9 H_2O$ Calcd: C 60.77, H 6.26, S 5.41 Found: C 60.45, H 6.45, S 5.41
157	2	$CH_2CH_2OSi(Ph)_2tBu$	$C_{30}H_{35}F_3O_5SSi \cdot 0.2 H_2O$ Calcd: C 60.42, H 5.98 Found: C 60.34, H 5.75
158	2		$C_{28}H_{23}Cl_2F_3N_2O_4S \cdot 0.4 H_2O$ Calcd: C 54.36, H 3.88, S 4.53 Found: C 54.03, H 3.76, S 4.69

174

Scheme 9B.

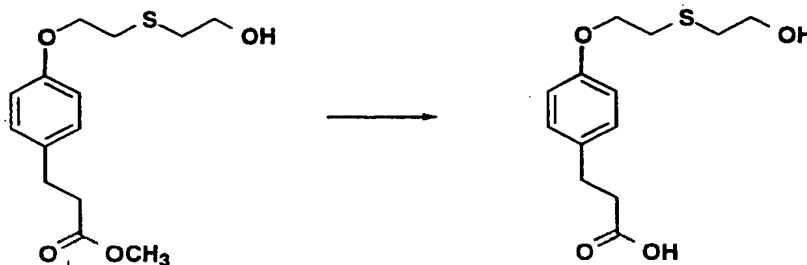


175

Example 1594-[4-[2-[2-Hydroxyethylthio]ethoxy]phenyl]-1,1,1-trifluoro butanone.5 3-[4-[2-(2-hydroxyethylthio)ethoxy]phenyl]propanoic acid, methyl ester

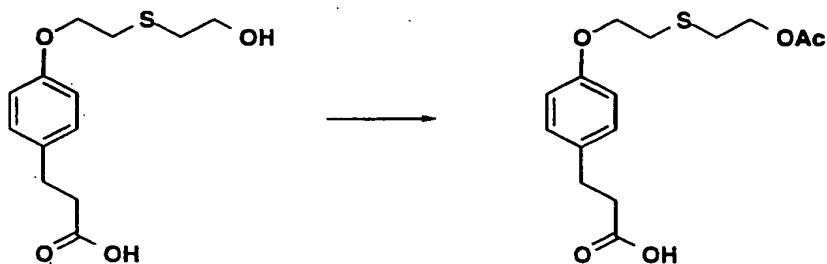
A solution of methyl 3-[4-hydroxyphenyl] propionate (30.0 g, 0.166 mol),
 10 2,2'-thiodiethanol (61.0 g, 0.50 mol) and triphenylphosphine (48.0 g, 0.183 mol) in dry benzene (450 ml) was treated at 22°C with diethyl azodicarboxylate (33.2 g, 0.19 mol) added dropwise over 10 min and the resulting mixture was stirred at 22°C for 5 h. The reaction mixture was then diluted with ether (300 ml) washed with water, saturated sodium
 15 bicarbonate and brine. After drying (magnesium sulfate) the solvent was evaporated in vacuo and the residue was chromatographed on silica gel (elution toluene-ethyl acetate 85:15) to give 37.64 g (79%) of the starting material as a white solid: mp 47-48°C.

Anal. Calcd. for $C_{14}H_{20}O_4S$: C 59.13, H 7.09. Found: C 58.94, H 7.04.

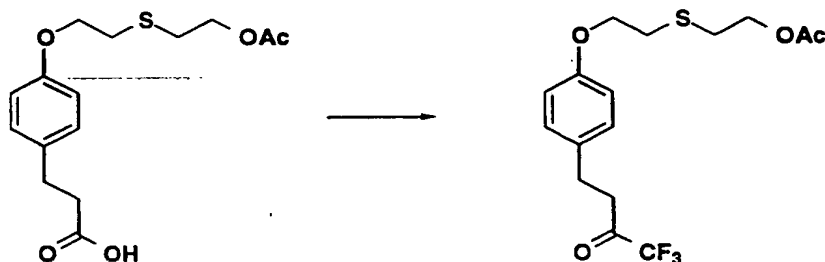
3-[4-[2-(2-hydroxyethylthio)ethoxy]phenyl] propanoic acid.

- 5 A solution of 3-[4-[2-(2-hydroxyethylthio)ethoxy]phenyl] propanoic acid, methyl ester (37.64 g, 0.132 mol) in 80% aqueous ethanol (300 ml) was treated with a solution of potassium hydroxide (17.0 g, 0.257 mol) in water (25 ml) and the resulting mixture was stirred at 22°C for 1 h. The solvent was then concentrated *in vacuo* and the residue was diluted with water
- 10 (200 ml) and dichloromethane (200 ml). The aqueous phase was then adjusted to pH 2 with 6N hydrochloric acid and extracted several times with dichloromethane. The combined organic extracts were washed with brine, dried (magnesium sulfate) and evaporated to give 35.67 g (100%) of the title material as a white solid: mp 64-65°C.
- 15 Anal. Calcd. for C₁₃H₁₈O₄S: C 57.76, H 6.71. Found: C 57.74, H 6.80.

177

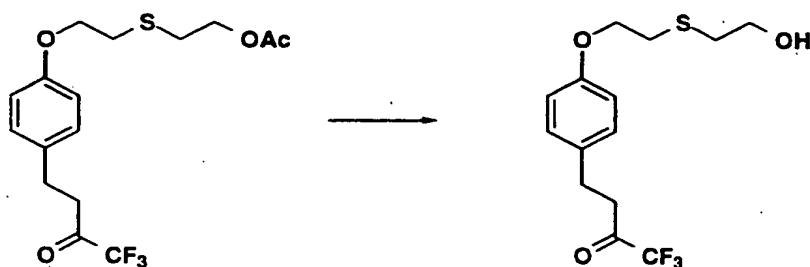
3-[4-[2-(2-acetoxyethylthio)ethoxy]phenyl] propanoic acid.

- 5 A solution of 3-[4-[2-(2-hydroxyethylthio)ethoxy]phenyl] propanoic acid, (35.67 g, 0.13 mol) in a mixture of toluene (500 ml) and acetic acid (500 ml) was treated with p-toluenesulfonic acid (1.2 g) and then heated under reflux using a Dean-Stark apparatus for 2 h. The cooled mixture was concentrated *in vacuo* and the residue was diluted with ethyl acetate,
- 10 washed with water and dried (magnesium sulfate). Evaporation of the solvent under vacuum gave a solid which was crystallized from hexane to give 36.13 g (88%) of title material as a white solid: mp 48-49°C.

4-[4-[2-(2-acetoxyethylthio)ethoxy]phenyl]-1,1,1-trifluoro-2-butanone.

- 5 A solution of 3-[4-[2-(2-acetoxyethylthio)ethoxy]phenyl] propanoic acid, (36.13 g, 0.115 mol) in dichloromethane (250 ml) was treated with oxalyl chloride (24 ml) and a drop of N,N-dimethylformamide. After 1 h at 25°C, the solvent and excess reagent were evaporated *in vacuo*. The residual oil was dissolved in toluene (250 ml) cooled to 0°C and treated with
- 10 trifluoroacetic anhydride (49.0 ml, 0.347 mol). Then pyridine (19.0 ml, 0.232 mol) was added dropwise over 30 min and the resulting mixture was stirred at 22°C for 3 h. The solution was then cooled again to 0°C, treated dropwise with water (70 ml) and then stirred at 22°C for 30 min. The solution was then diluted with ethyl acetate, washed with water, saturated
- 15 sodium bicarbonate, brine and dried (magnesium sulfate). Evaporation of the solvent *in vacuo* gave an oil which was chromatographed on silica gel. Elution with a mixture of dichloromethane and ethyl acetate (0 - 2%) gave 26.10 g (62%) of the title material as an oil.

179

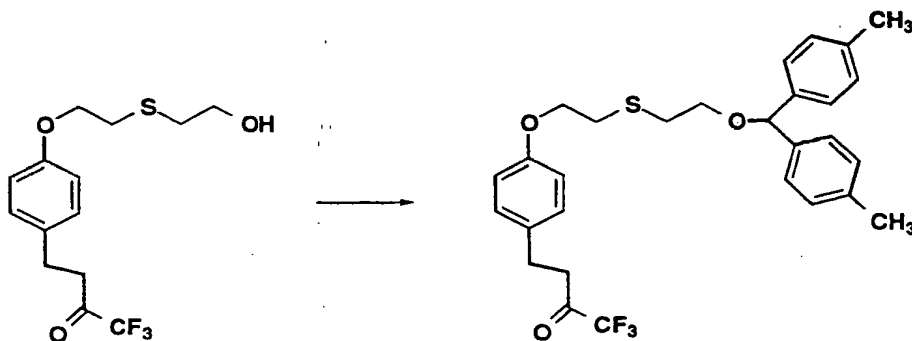
4-[4-[2-(2-hydroxyethylthio)ethoxy]phenyl]-1,1,1-trifluoro-2-butanone.

- 5 A solution of 4-[4-[2-(2-acetoxyethylthio)ethoxy]phenyl]-1,1,1-trifluoro-2-butanone (26.10 g, 71.6 mmol) in ethanol (275 ml) was treated at 22°C with a solution of potassium hydroxide (6.0 g, 91.0 mmol) in water (70 ml) and the resulting mixture was stirred for 30 min. The solvent was then evaporated *in vacuo* and the residual oil was dissolved in ethyl acetate,
- 10 washed with water, brine and dried (magnesium sulfate). Evaporation of the solvent gave 23.0 g (100%) of the title material as an oil.
- Anal. Calcd. for C₁₄H₁₇F₃O₃S. 0.3 H₂O: C 51.31, H 5.41. Found: C 51.11, H 5.42.

180

Example 160**4-[4-[2-[2-[Bis(4-methylphenyl)methoxy]ethylthio]ethoxy]phenyl]-1,1,1-trifluoro-2-butanone.**

5



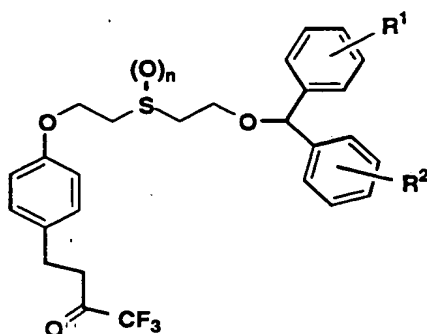
A solution of 4-[4-(2-hydroxyethylthio)ethoxy]phenyl]-1,1,1-trifluoro-2-butanone (1.20 g, 3.72 mmol), 4,4'-dimethylbenzhydrol (0.95 g, 4.47 mmol) and p-toluenesulfonic acid (0.035 g) in toluene (20 ml) was heated under reflux for 15 min. The cooled reaction mixture was diluted with ethyl acetate, washed with saturated sodium bicarbonate, brine and dried (magnesium sulfate). Evaporation of the solvent *in vacuo* and chromatography of the residue on silica gel (elution with a gradient of ethyl acetate 20-40% in hexane) gave 1.81 g (94%) of the title material as an oil.

Anal. Calcd. for $C_{29}H_{31}F_3O_3S$: C 67.42, H 6.05. Found: C 67.43, H 6.08.

The following compounds may be prepared by the general procedure of Scheme 9B.

20

181

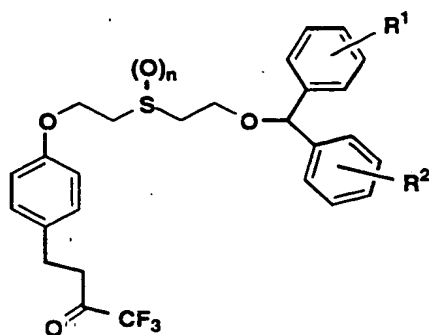
Table 9B

Exp. #	n	R ¹	R ²	Analysis
161	0	H	H	C ₂₇ H ₂₇ F ₃ O ₃ S. H ₂ O Calcd: C 64.02, H 5.77 Found: C 63.90, H 5.50
162	1	H	H	C ₂₇ H ₂₇ F ₃ O ₄ S.0.6 H ₂ O Calcd: C 62.90, H 5.52 Found: C 62.89, H 5.57
163	2	H	H	C ₂₇ H ₂₇ F ₃ O ₅ S. 0.6 H ₂ O Calcd: C 61.03, H 5.35 Found: C 60.99, H 5.12
164	1	p-CH ₃	p-CH ₃	C ₂₉ H ₃₁ F ₃ O ₄ S. 0.6 H ₂ O Calcd: C 64.10, H 5.97 Found: C 64.20, H 5.88
165	2	p-CH ₃	p-CH ₃	C ₂₉ H ₃₁ F ₃ O ₅ S. 0.5 H ₂ O Calcd: C 62.46, H 5.78 Found: C 62.40, H 5.70

A82

166	0	p-CH ₂ CH ₃	H	C ₂₉ H ₃₁ F ₃ O ₃ S. 0.3 H ₂ O Calcd: C 66.72, H 6.10 Found: C 66.84, H 5.96
167	1	p-CH ₂ CH ₃	H	C ₂₉ H ₃₁ F ₃ O ₄ S. 0.5 H ₂ O Calcd: C 64.31, H 5.96 Found: C 64.38, H 6.08
168	2	p-CH ₂ CH ₃	H	C ₂₉ H ₃₁ F ₃ O ₅ S. 0.3 H ₂ O Calcd: C 62.87, H 5.75 Found: C 62.88, H 5.73
169	0	p-tBu	H	C ₃₁ H ₃₅ F ₃ O ₃ S. 0.4 H ₂ O Calcd: C 67.47, H 6.54 Found: C 67.51, H 6.41
170	1	p-tBu	H	C ₃₁ H ₃₅ F ₃ O ₄ S. 0.5 H ₂ O Calcd: C 65.36, H 6.37 Found: C 65.37, H 6.29
171	2	p-tBu	H	C ₃₁ H ₃₅ F ₃ O ₅ S. 0.4 H ₂ O Calcd: C 63.77, H 6.18 Found: C 63.84, H 5.81
172	0	p-Cl	H	C ₂₇ H ₂₆ ClF ₃ O ₃ S Calcd: C 62.01, H 5.01 Found: C 62.40, H 4.80
173	2	p-Cl	H	C ₂₇ H ₂₆ ClF ₃ O ₅ S Calcd: C 58.43, H 4.72 Found: C 58.14, H 4.71

181

Table 9B

Exp. #	n	R ¹	R ²	Analysis
161	0	H	H	C ₂₇ H ₂₇ F ₃ O ₃ S. H ₂ O Calcd: C 64.02, H 5.77 Found: C 63.90, H 5.50
162	1	H	H	C ₂₇ H ₂₇ F ₃ O ₄ S.0.6 H ₂ O Calcd: C 62.90, H 5.52 Found: C 62.89, H 5.57
163	2	H	H	C ₂₇ H ₂₇ F ₃ O ₅ S. 0.6 H ₂ O Calcd: C 61.03, H 5.35 Found: C 60.99, H 5.12
164	1	p-CH ₃	p-CH ₃	C ₂₉ H ₃₁ F ₃ O ₄ S. 0.6 H ₂ O Calcd: C 64.10, H 5.97 Found: C 64.20, H 5.88
165	2	p-CH ₃	p-CH ₃	C ₂₉ H ₃₁ F ₃ O ₅ S. 0.5 H ₂ O Calcd: C 62.46, H 5.78 Found: C 62.40, H 5.70

A82

166	0	p-CH ₂ CH ₃	H	C ₂₉ H ₃₁ F ₃ O ₃ S. 0.3 H ₂ O Calcd: C 66.72, H 6.10 Found: C 66.84, H 5.96
167	1	p-CH ₂ CH ₃	H	C ₂₉ H ₃₁ F ₃ O ₄ S. 0.5 H ₂ O Calcd: C 64.31, H 5.96 Found: C 64.38, H 6.08
168	2	p-CH ₂ CH ₃	H	C ₂₉ H ₃₁ F ₃ O ₅ S. 0.3 H ₂ O Calcd: C 62.87, H 5.75 Found: C 62.88, H 5.73
169	0	p-tBu	H	C ₃₁ H ₃₅ F ₃ O ₃ S. 0.4 H ₂ O Calcd: C 67.47, H 6.54 Found: C 67.51, H 6.41
170	1	p-tBu	H	C ₃₁ H ₃₅ F ₃ O ₄ S. 0.5 H ₂ O Calcd: C 65.36, H 6.37 Found: C 65.37, H 6.29
171	2	p-tBu	H	C ₃₁ H ₃₅ F ₃ O ₅ S. 0.4 H ₂ O Calcd: C 63.77, H 6.18 Found: C 63.84, H 5.81
172	0	p-Cl	H	C ₂₇ H ₂₆ ClF ₃ O ₃ S Calcd: C 62.01, H 5.01 Found: C 62.40, H 4.80
173	2	p-Cl	H	C ₂₇ H ₂₆ ClF ₃ O ₅ S Calcd: C 58.43, H 4.72 Found: C 58.14, H 4.71

183

174	0	m-Cl	H	C₂₇H₂₆ClF₃O₃S Calcd: C 62.01, H 5.01 Found: C 61.97, H 5.04
175	1	m-Cl	H	C₂₇H₂₆ClF₃O₄S.0.5H₂O Calcd: C 59.18, H 4.97 Found: C 59.15, H 4.80
176	2	m-Cl	H	C₂₇H₂₆ClF₃O₅S.0.5H₂O Calcd: C 57.50, H 4.63 Found: C 57.51, H 4.65
177	0	m-Cl p-Cl	H	C₂₇H₂₅Cl₂F₃O₃S.0.2H₂O Calcd: C 57.80, H 4.56 Found: C 57.93, H 4.59
178	2	m-Cl p-Cl	H	C₂₇H₂₅Cl₂F₃O₄S.0.5H₂O Calcd: C 54.19, H 4.38 Found: C 54.20, H 4.35
179	2	m-Cl	m-Cl	C₂₇H₂₅Cl₂F₃O₄S. H₂O Calcd: C 53.38, H 4.48 Found: C 53.15, H 4.14
180	0	p-F	p-F	C₂₇H₂₅F₅O₃S Calcd: C 61.82, H 4.80, S 6.11 Found: C 61.90, H 4.66, S 6.07
181	1	p-F	p-F	C₂₇H₂₅F₅O₄S Calcd: C 57.59, H 4.92, S 5.69 Found: C 57.55, H 4.66, S 5.83

184

182	2	p-F	p-F	$C_{27}H_{25}F_5O_5S \cdot 0.25 H_2O$ Calcd: C 57.80, H 4.58, S 5.71 Found: C 57.66, H 4.34, S 5.83
183	0	p-Br	p-Br	$C_{27}H_{25}Br_2F_3O_3S$ Calcd: C 50.17, H 3.90, S 4.96 Found: C 49.97, H 3.88, S 5.06
184	1	p-Br	p-Br	$C_{27}H_{25}Br_2F_3O_4S \cdot 1.2 H_2O$ Calcd: C 47.41, H 4.04, S 4.69 Found: C 47.22, H 3.77, S 4.74
185	2	p-Br	p-Br	$C_{27}H_{25}Br_2F_3O_5S \cdot H_2O$ Calcd: C 46.57, H 3.91, S 4.60 Found: C 46.71, H 3.87, S 4.71
186	2	penta-F	penta-F	$C_{27}H_{17}F_{13}O_5S \cdot 0.7 H_2O$ Calcd: C 45.48, H 2.60 Found: C 45.53, H 2.49
187	0	p-Cl	p-Ph	$C_{33}H_{30}ClF_3O_3S$ Calcd: C 66.16, H 5.05 Found: C 66.08, H 4.81
188	1	p-Cl	p-Ph	$C_{33}H_{30}ClF_3O_4S \cdot 0.6 H_2O$ Calcd: C 63.32, H 5.02 Found: C 63.08, H 4.75
189	2	p-Cl	p-Ph	$C_{33}H_{30}ClF_3O_5S \cdot 0.8 H_2O$ Calcd: C 61.40, H 4.93 Found: C 61.27, H 4.46

185

190	0	m-NO ₂	m-NO ₂	<p>C₂₇H₂₅F₃N₂O₇S. 0.8 H₂O</p> <p>Calcd: C 54.69, H 4.52, N 4.72, S 5.41</p> <p>Found: C 54.57, H 4.36, N 4.76, S 5.36</p>
191	1	m-NO ₂	m-NO ₂	<p>C₂₇H₂₅F₃N₂O₈S.H₂O</p> <p>Calcd: C 52.94, H 4.44, N 4.57, S 5.23</p> <p>Found: C 52.97, H 4.22, N 4.59, S 5.38</p>
192	2	m-NO ₂	m-NO ₂	<p>C₂₇H₂₅F₃N₂O₉S. 0.5 H₂O</p> <p>Calcd: C 52.34, H 4.23, N 4.52, S 5.18</p> <p>Found: C 52.29, H 4.02, N 4.47, S 5.39</p>
193	0	p-Cl m-NO ₂	H	<p>C₂₇H₂₅ClF₃NO₅S</p> <p>Calcd: C 57.09, H 4.44, N 2.47</p> <p>Found: C 57.12, H 4.47, N 2.73</p>
194	2	p-Cl m-NO ₂	H	<p>C₂₇H₂₅ClF₃NO₇S. 0.3 H₂O</p> <p>Calcd: C 53.37, H 4.26, N 2.31</p> <p>Found: C 53.56, H 4.26, N 2.47</p>
195	0	p-Cl m-NO ₂	p-Cl m-NO ₂	<p>C₂₇H₂₃Cl₂F₃N₂O₇S. 0.3 H₂O</p> <p>Calcd: C 49.67, H 3.64, N 4.29, S 4.91</p> <p>Found: C 49.40, H 3.47, N 4.59, S 4.81</p>

186

196	1	p-Cl m-NO ₂	p-Cl m-NO ₂	C ₂₇ H ₂₃ Cl ₂ F ₃ N ₂ O ₈ S. 0.3 H ₂ O Calcd: C 48.49, H 3.56, N 4.19, S 4.79 Found: C 48.52, H 3.73, N 4.15, S 4.85
197	2	p-Cl m-NO ₂	p-Cl m-NO ₂	C ₂₇ H ₂₃ Cl ₂ F ₃ N ₂ O ₉ S Calcd: C 47.73, H 3.41, N 4.12, S 4.72 Found: C 47.57 H 3.31, N 4.14, S 4.76
198	0	m-OCH ₃	m-OCH ₃	C ₂₉ H ₃₁ F ₃ O ₅ S. 0.5 H ₂ O Calcd: C 62.46, H 5.78 Found: C 62.51, H 5.79
199	1	m-OCH ₃	m-OCH ₃	C ₂₉ H ₃₁ F ₃ O ₆ S. 0.9 H ₂ O Calcd: C 59.97, H 5.69 Found: C 59.98, H 5.53
200	2	m-OCH ₃	m-OCH ₃	C ₂₉ H ₃₁ F ₃ O ₇ S. 0.2 H ₂ O Calcd: C 59.62, H 5.42 Found: C 59.55, H 5.47
201	0	p-OCH ₃	p-OCH ₃	C ₂₉ H ₃₁ F ₃ O ₅ S. 0.1 H ₂ O Calcd: C 63.28, H 5.71 Found: C 62.90, H 5.60
202	1	p-OCH ₃	p-OCH ₃	C ₂₉ H ₃₁ F ₃ O ₆ S. 0.6 H ₂ O Calcd: C 60.53, H 5.64, S 5.57 Found: C 60.41, H 5.54, S 5.62

185

190	0	m-NO ₂	m-NO ₂	<p>C₂₇H₂₅F₃N₂O₇S. 0.8 H₂O</p> <p>Calcd: C 54.69, H 4.52, N 4.72, S 5.41</p> <p>Found: C 54.57, H 4.36, N 4.76, S 5.36</p>
191	1	m-NO ₂	m-NO ₂	<p>C₂₇H₂₅F₃N₂O₈S.H₂O</p> <p>Calcd: C 52.94, H 4.44, N 4.57, S 5.23</p> <p>Found: C 52.97, H 4.22, N 4.59, S 5.38</p>
192	2	m-NO ₂	m-NO ₂	<p>C₂₇H₂₅F₃N₂O₉S. 0.5 H₂O</p> <p>Calcd: C 52.34, H 4.23, N 4.52, S 5.18</p> <p>Found: C 52.29, H 4.02, N 4.47, S 5.39</p>
193	0	p-Cl m-NO ₂	H	<p>C₂₇H₂₅ClF₃NO₅S</p> <p>Calcd: C 57.09, H 4.44, N 2.47</p> <p>Found: C 57.12, H 4.47, N 2.73</p>
194	2	p-Cl m-NO ₂	H	<p>C₂₇H₂₅ClF₃NO₇S. 0.3 H₂O</p> <p>Calcd: C 53.37, H 4.26, N 2.31</p> <p>Found: C 53.56, H 4.26, N 2.47</p>
195	0	p-Cl m-NO ₂	p-Cl m-NO ₂	<p>C₂₇H₂₃Cl₂F₃N₂O₇S. 0.3 H₂O</p> <p>Calcd: C 49.67, H 3.64, N 4.29, S 4.91</p> <p>Found: C 49.40, H 3.47, N 4.59, S 4.81</p>

186

196	1	p-Cl m-NO ₂	p-Cl m-NO ₂	C ₂₇ H ₂₃ Cl ₂ F ₃ N ₂ O ₈ S. 0.3 H ₂ O Calcd: C 48.49, H 3.56, N 4.19, S 4.79 Found: C 48.52, H 3.73, N 4.15, S 4.85
197	2	p-Cl m-NO ₂	p-Cl m-NO ₂	C ₂₇ H ₂₃ Cl ₂ F ₃ N ₂ O ₉ S Calcd: C 47.73, H 3.41, N 4.12, S 4.72 Found: C 47.57 H 3.31, N 4.14, S 4.76
198	0	m-OCH ₃	m-OCH ₃	C ₂₉ H ₃₁ F ₃ O ₅ S. 0.5 H ₂ O Calcd: C 62.46, H 5.78 Found: C 62.51, H 5.79
199	1	m-OCH ₃	m-OCH ₃	C ₂₉ H ₃₁ F ₃ O ₆ S. 0.9 H ₂ O Calcd: C 59.97, H 5.69 Found: C 59.98, H 5.53
200	2	m-OCH ₃	m-OCH ₃	C ₂₉ H ₃₁ F ₃ O ₇ S. 0.2 H ₂ O Calcd: C 59.62, H 5.42 Found: C 59.55, H 5.47
201	0	p-OCH ₃	p-OCH ₃	C ₂₉ H ₃₁ F ₃ O ₅ S. 0.1 H ₂ O Calcd: C 63.28, H 5.71 Found: C 62.90, H 5.60
202	1	p-OCH ₃	p-OCH ₃	C ₂₉ H ₃₁ F ₃ O ₆ S. 0.6 H ₂ O Calcd: C 60.53, H 5.64, S 5.57 Found: C 60.41, H 5.54, S 5.62

487

203	2	p-OCH ₃	p-OCH ₃	C ₂₉ H ₃₁ F ₃ O ₇ S. 0.7 H ₂ O Calcd: C 58.72, H 5.51, S 5.40 Found: C 58.5, H 5.48, S 5.47
204	0	p-O Allyl	p-O Allyl	C ₃₃ H ₃₅ F ₃ O ₅ S Calcd: C 65.98, H 5.87, S 5.34 Found: C 65.89, H 5.93, S 5.36
205	1	p-OAllyl	p-O Allyl	C ₃₃ H ₃₅ F ₃ O ₆ S. 0.6 H ₂ O Calcd: C 63.17, H 5.81, S 5.11 Found: C 63.10, H 5.69, S 5.14
206	2	p-O Allyl	p-O Allyl	C ₃₃ H ₃₅ F ₃ O ₇ S. 0.4 H ₂ O Calcd: C 61.94, H 5.64, S 5.01 Found: C 61.89, H 5.53, S 5.05
207	0	p-OCH ₃	H	C ₂₈ H ₂₉ F ₃ O ₄ S. 0.3 H ₂ O Calcd: C 64.18, H 5.69 Found: C 64.14, H 5.82
208	1	p-OCH ₃	H	C ₂₈ H ₂₉ F ₃ O ₅ S. 0.6 H ₂ O Calcd: C 61.66, H 5.58 Found: C 61.86, H 5.51
209	2	p-OCH ₃	H	C ₂₈ H ₂₉ F ₃ O ₆ S. 0.6 H ₂ O Calcd: C 59.91, H 5.42 Found: C 59.90, H 5.20
210	0	m-CF ₃	H	C ₂₈ H ₂₆ F ₆ O ₃ S Calcd: C 60.43, H 4.71 Found: C 60.43, H 4.54

188

211	1	m-CF ₃	H	C ₂₈ H ₂₆ F ₆ O ₄ S. 0.7 H ₂ O Calcd: C 57.47, H 4.72 Found: C 57.29, H 4.46
212	2	m-CF ₃	H	C ₂₈ H ₂₆ F ₆ O ₅ S. 0.5 H ₂ O Calcd: C 56.28, H 4.55 Found: C 56.28, H 4.53
213	0	p-CF ₃	H	C ₂₈ H ₂₆ F ₆ O ₃ S Calcd: C 60.43, H 4.71 Found: C 60.45, H 4.78
214	1	p-CF ₃	H	C ₂₈ H ₂₆ F ₆ O ₄ S. 0.5 H ₂ O Calcd: C 57.83, H 4.68 Found: C 57.82, H 4.57
215	2	p-CF ₃	H	C ₂₈ H ₂₆ F ₆ O ₅ S. 0.2 H ₂ O Calcd: C 56.79, H 4.49 Found: C 56.83, H 4.44
216	2	p-CF ₃	p-CF ₃	C ₂₉ H ₂₅ F ₉ O ₅ S. 0.2 H ₂ O Calcd: C 52.76, H 3.86 Found: C 52.63, H 3.87
217	2	m-CF ₃	m-CF ₃	C ₂₉ H ₂₅ F ₉ O ₅ S Calcd: C 53.05, H 3.84 Found: C 52.96, H 3.79
218	2	m-CF ₃	p-CF ₃	C ₂₉ H ₂₅ F ₉ O ₅ S. 0.4 H ₂ O Calcd: C 52.48, H 3.92 Found: C 52.43, H 3.90

159

219	0	p-OCH ₃	p-Cl	C ₂₈ H ₂₈ ClF ₃ O ₄ S Calcd: C 60.81, H 5.10 Found: C 60.67, H 5.07
220	1	p-OCH ₃	p-Cl	C ₂₈ H ₂₈ ClF ₃ O ₅ S. 0.7 H ₂ O Calcd: C 57.82, H 5.09 Found: C 57.82, H 5.05
221	2	p-OCH ₃	p-Cl	C ₂₈ H ₂₈ ClF ₃ O ₆ S. 0.4 H ₂ O Calcd: C 56.79, H 4.90 Found: C 56.77, H 4.81
222	0	p-OCH ₃	p-F	C ₂₈ H ₂₈ F ₄ O ₄ S Calcd: C 62.68, H 5.26 Found: C 62.61, H 5.30
223	1	p-OCH ₃	p-F	C ₂₈ H ₂₈ F ₄ O ₅ S. 0.4 H ₂ O Calcd: C 60.08, H 5.19 Found: C 60.05, H 5.24
224	2	p-OCH ₃	p-F	C ₂₈ H ₂₈ F ₄ O ₆ S. 0.3 H ₂ O Calcd: C 58.59, H 5.02 Found: C 58.50, H 5.10
225	0	m-Cl o-OCH ₃	H	C ₂₈ H ₂₈ ClF ₃ O ₄ S Calcd: C 60.81, H 5.10 Found: C 60.70, H 5.20
226	1	m-Cl o-OCH ₃	H	C ₂₈ H ₂₈ ClF ₃ O ₅ S. 0.3 H ₂ O Calcd: C 58.55, H 5.02 Found: C 58.53, H 4.72

190

227	2	m-Cl o-OCH ₃	H	C ₂₈ H ₂₈ ClF ₃ O ₆ S. 0.4 H ₂ O Calcd: C 56.79, H 4.990 Found: C 56.73, H 4.95
228	0	p-Cl	p-SCH ₃	C ₂₈ H ₂₈ ClF ₃ O ₃ S ₂ Calcd: C 59.09, H 4.96 Found: C 59.06, H 5.00
229	1	p-Cl	p-SCH ₃	C ₂₈ H ₂₈ ClF ₃ O ₄ S ₂ . 0.8 H ₂ O Calcd: C 56.10, H 4.98 Found: C 56.10, H 4.79
230	2	p-Cl	p-SCH ₃	C ₂₈ H ₂₈ ClF ₃ O ₅ S ₂ . 0.2 H ₂ O Calcd: C 55.62, H 4.73 Found: C 55.59, H 4.66
231	1	p-Cl	p-SOCH ₃	C ₂₈ H ₂₈ ClF ₃ O ₅ S ₂ . H ₂ O Calcd: C 54.32, H 4.88 Found: C 54.31, H 5.06
232	2	p-Cl	p-SOCH ₃	C ₂₈ H ₂₈ ClF ₃ O ₆ S ₂ . H ₂ O Calcd: C 52.95, H 4.76 Found: C 53.05, H 4.68
233	2	p-Cl	p-SO ₂ CH ₃	C ₂₈ H ₂₈ ClF ₃ O ₇ S ₂ . 0.4 H ₂ O Calcd: C 52.52, H 4.53 Found: C 52.53, H 4.55
234	2	p-SCH ₃	p-SCH ₃	C ₂₉ H ₃₁ F ₃ O ₅ S ₃ . 0.4 H ₂ O Calcd: C 56.18, H 5.17 Found: C 56.11, H 5.06

191

235	0	p-SO ₂ N(CH ₃) ₂	H	C ₂₉ H ₃₂ F ₃ NO ₅ S ₂ · 0.3 H ₂ O Calcd: C 57.95, H 5.47, N 2.33, S 10.69 Found: C 58.10, H 5.41, N 2.49, S 10.29
236	2	p-SO ₂ N(CH ₃) ₂	H	C ₂₉ H ₃₂ F ₃ NO ₇ S ₂ · H ₂ O Calcd: C 53.94, H 5.31, N 2.17, S 9.93 Found: C 54.04, H 5.13, N 2.25, S 9.44
237	0	p-CO ₂ CH ₃	H	C ₂₉ H ₂₉ F ₃ O ₅ S · 0.7 H ₂ O Calcd: C 62.29, H 5.48 Found: C 62.15, H 5.07
238	1	p-CO ₂ CH ₃	H	C ₂₉ H ₂₉ F ₃ O ₆ S · 2 H ₂ O Calcd: C 58.19, H 5.56 Found: C 57.77, H 5.03
239	2	p-CO ₂ CH ₃	H	C ₂₉ H ₂₉ F ₃ O ₇ S · 0.3 H ₂ O Calcd: C 59.64, H 5.11 Found: C 59.66, H 4.87
240	0	m-CO ₂ CH ₃	H	C ₂₉ H ₂₉ F ₃ O ₅ S · 0.6 H ₂ O Calcd: C 62.49, H 5.46 Found: C 62.39, H 5.25
241	1	m-CO ₂ CH ₃	H	C ₂₉ H ₂₉ F ₃ O ₆ S · 1.3 H ₂ O Calcd: C 59.44, H 5.44 Found: C 59.17, H 5.14

192

242	2	m-CO ₂ CH ₃	H	C₂₉H₂₉F₃O₇S. H₂O Calcd: C 58.38, H 5.24 Found: C 58.03, H 4.87
243	2	m-CO ₂ H	H	C₂₈H₂₇F₃O₇S. 1.9 H₂O Calcd: C 56.16, H 5.18 Found: C 56.31, H 4.63

5

10

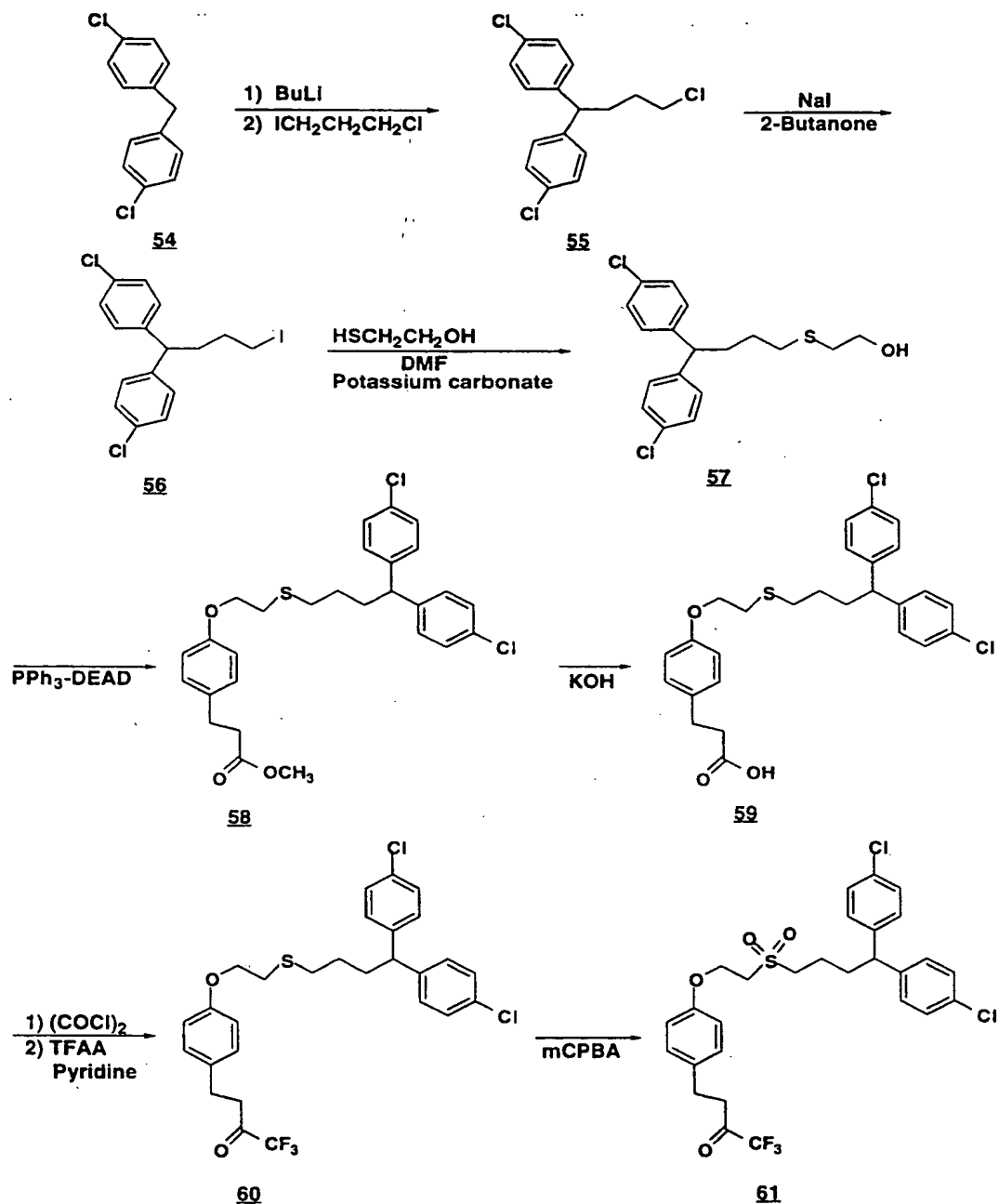
15

20

193

Example 244Scheme 9C

5

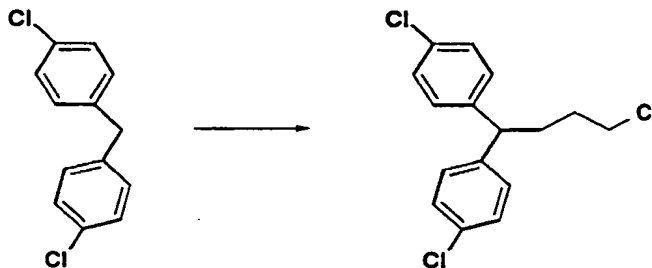


194

4-[4-[2-[4-Bis(4-methylphenyl)butylsulfonyl]ethoxy]phenyl-1,1,1-trifluoro-2-butanone.

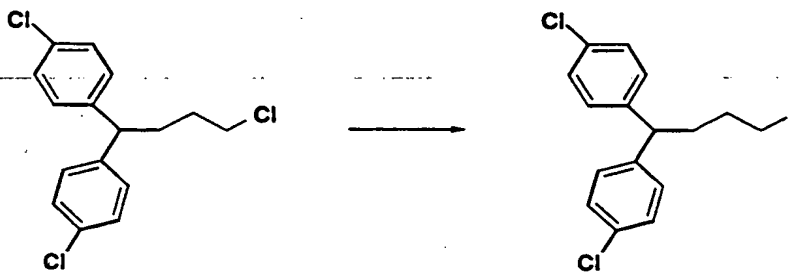
1-Chloro-4,4-di-(4-chlorophenyl)butane

5



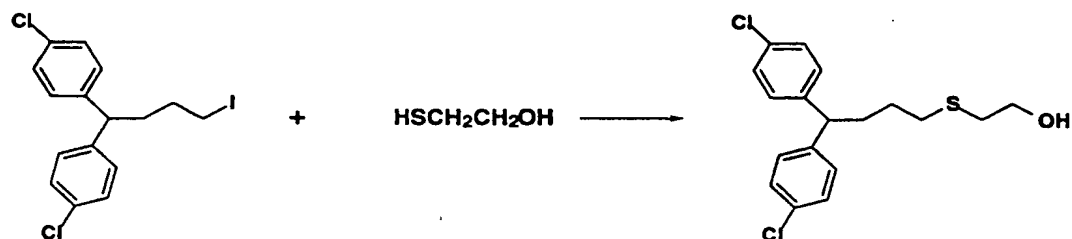
A solution of 4,4'-dichlorodiphenylmethane (4.37 g, 18.4 mmol) (Blackwell, J. et al, J. Chem. Soc., 1961, 1405) in dry tetrahydrofuran (50 ml) was treated at 0°C with butyllithium (12.1 ml of 1.6 M, 19.36 mmol) added dropwise over 15 min. After 15 min, the red solution was then added dropwise to a cold (-78°C) solution of 1-chloro-3-iodopropane (15.0 g, 73.4 mmol) in dry tetrahydrofuran (120 ml). After 20 min at -78°C, the reaction mixture was quenched by the addition of saturated ammonium chloride (100 ml) and diluted with toluene. The organic phase was washed with brine and dried. The oil obtained after evaporation of the solvent was purified on silica gel (elution hexane-toluene 85:15) and distilled under vacuum to give 2.54 g (44%) of the title material as a clear oil: bp 110-130°C/1.5 torr (air bath temperature).

195

1-Iodo-4,4-di-(4-chlorophenyl)butane

- 5 A solution of methyl 1-chloro-4,4-di-(4-chlorophenyl)butane (1.77 g, 5.64 mmol) in 2-butanone (20 ml) was treated with sodium iodide (1.5 g) and heated under reflux for 18 h. The solid formed was filtered, the filtrate was evaporated and purified on silica gel (elution hexane-toluene 96:5) to give 2.13 g (93%) of the title material as a clear oil.

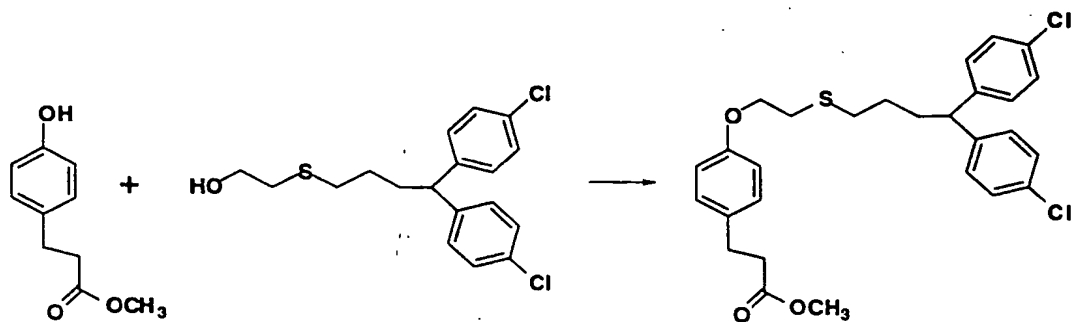
156

2-[4-Bis-(4-chlorophenyl)butylthio]ethanol

- 5 A solution of 1-iodo-4,4'-bis-(4-chlorophenyl)butane (3.22 g, 7.96 mmol) in N,N-dimethyl formamide (45 ml) was treated at 22°C with powdered anhydrous potassium carbonate (2.2 g) followed by 2-mercaptoethanol (0.71 g, 9.20 mmol) and the resulting mixture was stirred at 22°C for 18 h. The reaction mixture was then diluted with toluene (400 ml) washed with
- 10 water and brine and dried over anhydrous magnesium sulfate. After evaporation of the solvent, the residue was chromatographed on silica gel (elution toluene-ethyl acetate 8:2) to give 2.58 g (92%) of the title material as a clear oil.
- Anal. Calcd. for C₁₈H₂₀Cl₂OS: C 60.84, H 5.67, S 9.02. Found: C 61.12, H
- 15 5.75, S 9.28.

197

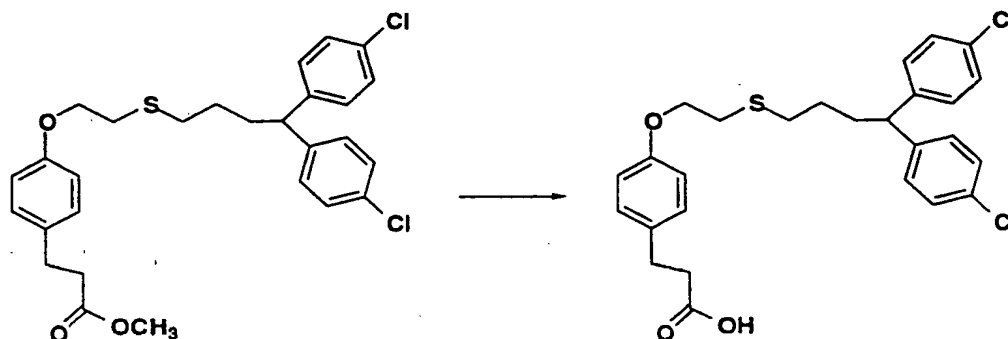
3-[4-[2-[4-Bis-(4-chlorophenyl)butylthio]ethoxy]phenyl]propionic acid,
methyl ester



5

A solution of methyl 3-(4-hydroxyphenyl)propionate (1.22 g, 6.77 mmol),
2-[4-bis-(4-chlorophenyl)butylthio]ethanol (2.58 g, 7.26 mmol) and
triphenylphosphine (1.95 g, 7.43 mmol) in dry benzene (30 ml) was treated
at 22°C with diethyl azodicarboxylate (1.29 g, 7.41 mmol) added dropwise
over 10 min. After 3 h at 22°C, the solvent was evaporated and the
residue was chromatographed on silica gel (elution hexane ethyl acetate,
84:16) to give 3.17 g (91%) of the title material as a clear oil.
Anal. Calcd. for $C_{28}H_{30}Cl_2O_3S$: C 64.99, H 5.84, S 6.20. Found: C 65.01, H
5.86, S 6.38.

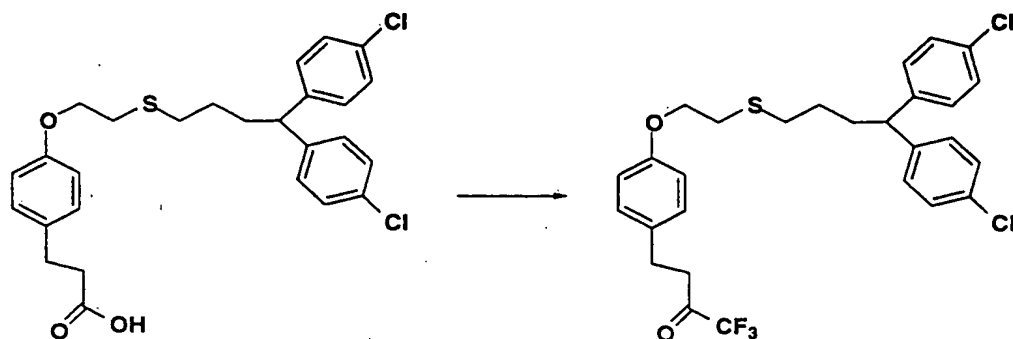
198

3-[4-[2-[4-Bis-(4-chlorophenyl)butylthio]ethoxy]phenyl]propionic acid.

- 5 A suspension of 3-[4-[2-[4-bis-(4-chlorophenyl)butylthio]ethoxy]phenyl]propionic acid, methyl ester (3.09 g, 5.98 mmol) in ethanol (25 ml) was treated with a solution of potassium hydroxide (0.8 g, 14.3 mmol) in water (9.5 ml) and the resulting mixture was maintained at 35°C for 2 h. The pH of the solution was then adjusted
- 10 to 4.0 with 1N hydrochloric acid and the mixture was extracted with dichloromethane. The organic extract was dried (magnesium sulfate) and evaporated to give a white solid. Recrystallization from cyclohexane gave 2.93 g (97%) of the title material as a white solid: mp 89-92°C.

199

4-[4-[2-[4-Bis-(4-chlorophenyl)butylthio]ethoxy]phenyl]-1,1,1-trifluoro-2-butanone.



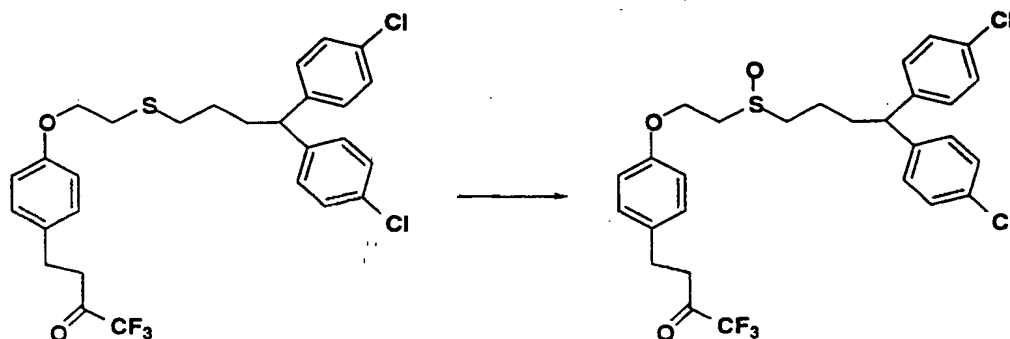
5

- A solution of 3-[4-[2-[4-bis-(4-chlorophenyl)butylthio]ethoxy]phenyl]propionic acid (2.85 g, 5.66 mmol) in dichloromethane (25 ml) was treated with oxalyl chloride (1.65 g, 13.0 mmol) and a small drop of N,N-dimethylformamide. After 1 h at 22°C, the solvent and excess reagent were evaporated *in vacuo* and the residual acid chloride was dissolved in dry toluene (85 ml). The solution was then cooled to 0°C and treated with trifluoroacetic anhydride (3.57 g, 17.0 mmol) in dry toluene (15 ml) added dropwise over 10 min. After 3.5 h at 22°C, the mixture was cooled again to 0°C and treated dropwise with water (5 ml) and stirred for 15 min. The reaction mixture was then diluted with toluene (200 ml), washed with saturated sodium bicarbonate, brine and dried (magnesium sulfate). Evaporation of the solvent gave an oil which was chromatographed on silica gel. Elution with a mixture of hexane and ethyl acetate (75:25) gave 2.62 g (83%) of the title material as an oil.
- Anal. Calcd. for $C_{28}H_{27}Cl_2F_3O_2S$: C 60.54, H 4.90, S 5.77. Found: C 60.43, H 4.85, S 5.88.

20

200

4-[4-[2-[4-Bis-(4-chlorophenyl)butylsulfinyl]ethoxy]phenyl]-1,1,1-trifluoro-2-butanone.

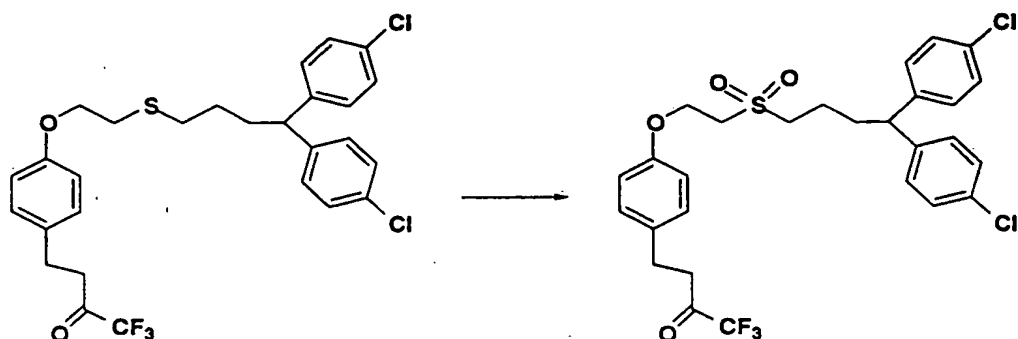


5

- A solution of 4-[4-[2-[4-bis-(4-chlorophenyl)butylthio]ethoxy]phenyl]-1,1,1-trifluoro-2-butanone (0.741 g, 1.33 mmol) in methanol (35 ml) was treated with a solution of sodium periodate (0.32 g, 1.5 mmol) in water (1.5 ml) and the resulting mixture was stirred at 22°C for 18 h. The solid formed
- 10 was filtered and the filtrate was evaporated *in vacuo*. The residue was diluted with ethyl acetate, washed with saturated sodium bicarbonate, brine and dried (magnesium sulfate). Evaporation of the solvent *in vacuo* gave an oil which was chromatographed on silica gel. Elution with a gradient of ethyl acetate in dichloromethane (40 - 90%) gave 0.654 g
- 15 (86%) of the title material as a white solid: mp 31-35°C.
- Anal. Calcd. for C₂₈H₂₇Cl₂F₃O₃S. 0.4 H₂O: C 58.12, H 4.84, S 5.54. Found: C 58.05, H 4.97, S 5.73.

2c1

4-[4-[2-[4-Bis-(4-chlorophenyl)butylsulfonyl]ethoxy]phenyl]-1,1,1-trifluoro-2-butanone.



5

A solution of 4-[4-[2-[4-bis-(4-chlorophenyl)butylthio]ethoxy]phenyl]-1,1,1-trifluoro-2-butanone (0.583 g, 1.05 mmol) in dichloromethane (25 ml) was treated at 22°C with m-chloroperbenzoic acid (0.592 g, 3.43 mmol) and the resulting mixture was stirred for 2 h. The reaction mixture was then diluted with ethyl acetate, washed with sodium bicarbonate, brine and dried (magnesium sulfate). Evaporation of the solvent *in vacuo* and chromatography of the residue on silica gel (elution ethyl acetate-hexane 1:1) gave 0.533 g (70%) of the title material as a clear oil.

10

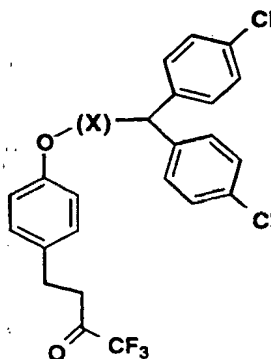
Anal. Calcd. for C₂₈H₂₇Cl₂F₃O₄S. 0.4 H₂O: C 56.55, H 4.71 S 5.39. Found: C 56.43, H 4.61, S 5.46.

15

20

202

The following compounds may be prepared by the general procedure shown above.

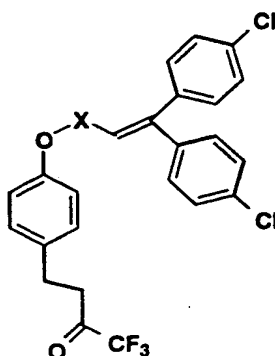
5 **Table 10**

Exp. #	X	Analysis
245	CH ₂ CH ₂ O	C ₂₅ H ₂₁ Cl ₂ F ₃ O ₃ Calcd: C 60.38, H 4.26 Found: C 60.28, H 4.18
246	CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ O	C ₂₈ H ₂₇ Cl ₂ F ₃ O ₃ Calcd: C 62.35, H 5.05 Found: C 62.19, H 5.12
247	CH ₂ CH ₂ CH ₂ SCH ₂ CH ₂ O	C ₂₈ H ₂₇ Cl ₂ F ₃ O ₃ S Calcd: C 58.85, H 4.76, S 5.61 Found: C 58.98, H 4.76, S 5.34
248	CH ₂ CH ₂ CH ₂ S(O)CH ₂ CH ₂ O	C ₂₈ H ₂₇ Cl ₂ F ₃ O ₄ S. 1.5 H ₂ O Calcd: C 54.73, H 4.92, N 5.22 Found: C 54.90, H 4.68, N 5.45

203

249	$\text{CH}_2\text{CH}_2\text{CH}_2\text{S}(\text{O}_2)\text{CH}_2\text{CH}_2\text{O}$	$\text{C}_{28}\text{H}_{27}\text{Cl}_2\text{F}_3\text{O}_5\text{S} \cdot 0.4 \text{ H}_2\text{O}$ Calcd: C 55.07, H 4.59, N 5.25 Found: C 55.0, H 4.44, N 5.46
250	$\text{CH}_2\text{CH}_2\text{SCH}_2\text{CH}_2\text{CH}_2\text{O}$	$\text{C}_{28}\text{H}_{27}\text{Cl}_2\text{F}_3\text{O}_3\text{S} \cdot 0.3 \text{ H}_2\text{O}$ Calcd: C 58.30, H 4.82, N 5.56 Found: C 58.31, H 4.52, N 5.11
251	$\text{CH}_2\text{CH}_2\text{S}(\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{O}$	$\text{C}_{28}\text{H}_{27}\text{Cl}_2\text{F}_3\text{O}_4\text{S} \cdot 0.8 \text{ H}_2\text{O}$ Calcd: C 55.87, H 4.79, N 5.33 Found: C 55.96, H 5.08, N 4.93
252	$\text{CH}_2\text{CH}_2\text{S}(\text{O}_2)\text{CH}_2\text{CH}_2\text{CH}_2\text{O}$	$\text{C}_{28}\text{H}_{27}\text{Cl}_2\text{F}_3\text{O}_5\text{S} \cdot 0.4 \text{ H}_2\text{O}$ Calcd: C 55.07, H 4.59, N 5.25 Found: C 55.07, H 4.10, N 4.78
253	$\text{CH}_2\text{CH}_2\text{SCH}_2\text{CH}=\text{CH}-\text{CH}_2$ (E)	$\text{C}_{29}\text{H}_{27}\text{Cl}_2\text{F}_3\text{O}_2\text{S}$ Calcd: C 61.38, H 4.80, N 5.65 Found: C 61.34, H 4.83, N 5.33
254	$\text{CH}_2\text{CH}_2\text{S}(\text{O})\text{CH}_2\text{CH}=\text{CH}-\text{CH}_2$ (E)	$\text{C}_{29}\text{H}_{27}\text{Cl}_2\text{F}_3\text{O}_3\text{S} \cdot 0.7 \text{ H}_2\text{O}$ Calcd: C 58.43, H 4.80, N 5.38 Found: C 58.28, H 4.91, N 5.2
255	$\text{CH}_2\text{CH}_2\text{S}(\text{O}_2)\text{CH}_2\text{CH}=\text{CH}-\text{CH}_2$ (E)	$\text{C}_{29}\text{H}_{27}\text{Cl}_2\text{F}_3\text{O}_4\text{S}$ Calcd: C 58.10, H 4.54, N 5.35 Found: C 57.79, H 4.39, N 5.17

204

Table 11

5

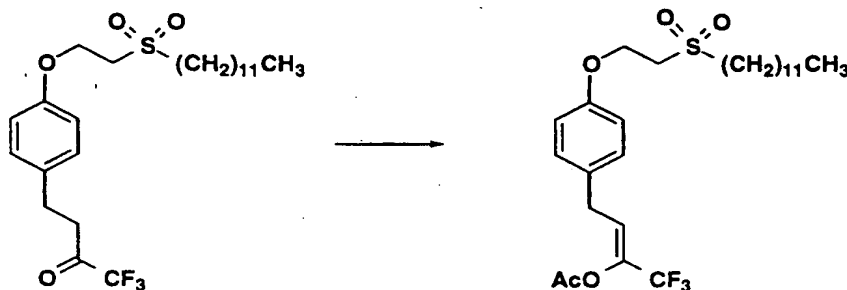
Exp. #	X	Analysis
256	CH ₂	C ₂₅ H ₁₉ Cl ₂ F ₃ O ₂ Calcd: C 62.65, H 4.00 Found: C 62.58, H 3.95
257	CH ₂ CH ₂ SCH ₂ CH ₂	C ₂₈ H ₂₅ Cl ₂ F ₃ O ₂ S. 0.7 H ₂ O Calcd: C 59.41, H 4.70, S 5.66 Found: C 59.30, H 4.40, S 5.67
258	CH ₂ CH ₂ S(O)CH ₂ CH ₂	C ₂₈ H ₂₅ Cl ₂ F ₃ O ₃ S. 0.6 H ₂ O Calcd: C 57.96, H 4.55, S 5.53 Found: C 58.29, H 4.53, S 5.13
259	CH ₂ CH ₂ S(O ₂)CH ₂ CH ₂	C ₂₈ H ₂₅ Cl ₂ F ₃ O ₄ S. 0.5 H ₂ O Calcd: C 56.57, H 4.41, S 5.39 Found: C 56.82, H 4.38, S 4.93

205

Example 260

(Z)-4-[4-[2-(Dodecylsulfonyl)ethoxy]phenyl]-1,1,1-trifluoro-2-acetoxy-2-butene.

5

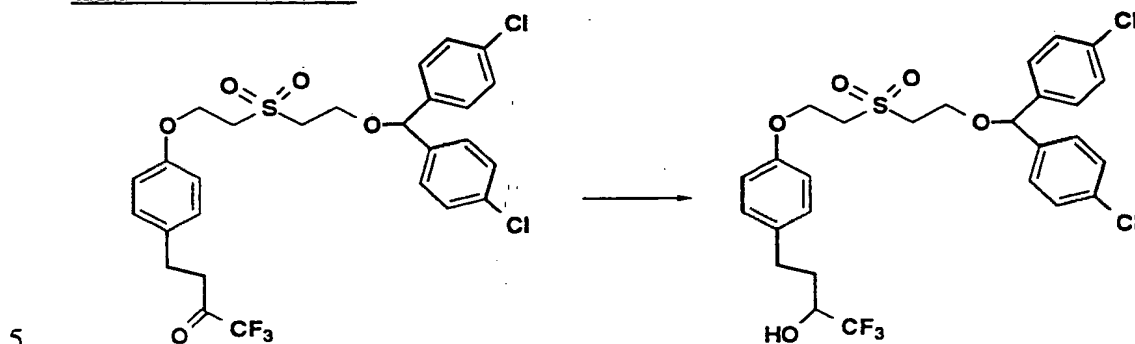


A solution of 4-[4-[2-(dodecylsulfonyl)ethoxy]phenyl]-1,1,1-trifluoro-2-butanone (1.10 g, 2.30 mmol) in dichloromethane (15 ml) was cooled to -25°C and treated with triethylamine (0.5 ml) and 4-dimethylaminopyridine (0.560 g, 4.58 mmol). Then acetic anhydride (0.65 ml, 6.9 mmol) was added and the resulting mixture was stirred at -25°C for 2.5 h. The solution was then diluted with ethyl acetate, washed with saturated sodium bicarbonate, dried (magnesium sulfate) and evaporated *in vacuo*. The residue was chromatographed on silica gel (elution toluene-ethyl acetate, 9:1) to give 0.94 g (78%) of a solid which was recrystallized from hexane to give white crystals: mp 48-49°C.

Anal. Calcd. for C₂₆H₃₉F₃O₅S: C 59.98, H 7.55, S 6.16. Found: C 59.95, H 7.51, S 6.38.

20

266

Example 261**4-[4-[2-[Bis(4-chlorophenyl)methoxy]ethylsulfonyl]ethoxy]phenyl]-1,1,1-trifluoro-2-butanol.**

A solution of 4-[4-[2-[bis(4-chlorophenyl)methoxy]ethylsulfonyl]ethoxy]phenyl]-1,1,1-trifluoro-2-butanone (0.77 g, 1.30 mmol) in tetrahydrofuran (45 ml) and water (5 ml) was treated with sodium borohydride (0.10 g, 2.6 mmol) and the resulting mixture was stirred at 22°C for 1 h. The reaction mixture was then diluted with ethyl acetate, washed successively with water and brine and then dried (magnesium sulfate). Evaporation of the solvent under reduced pressure gave an oil which was chromatographed on silica gel. Elution with a mixture of toluene and ethyl acetate (8:2) gave the title material as a white solid: mp 75-76°C.

Anal. Calcd. for $C_{27}H_{27}Cl_2F_3O_5S$: C 54.83, H 4.60, S 5.42. Found: C 54.84, H 4.39, S 5.07.

20

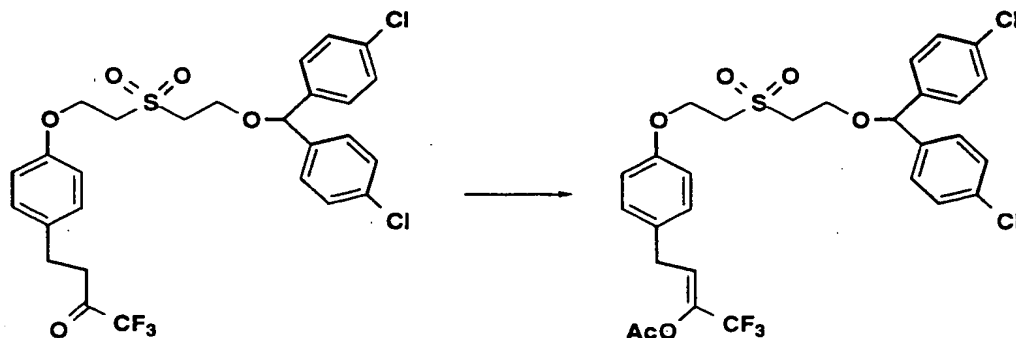
25

207

Example 262

(Z)-4-[4-[2-[Bis-(4-chlorophenyl)methoxy]ethylsulfonyl]ethoxy]phenyl]-1,1,1-trifluoro-2-acetoxy-2-butene.

5

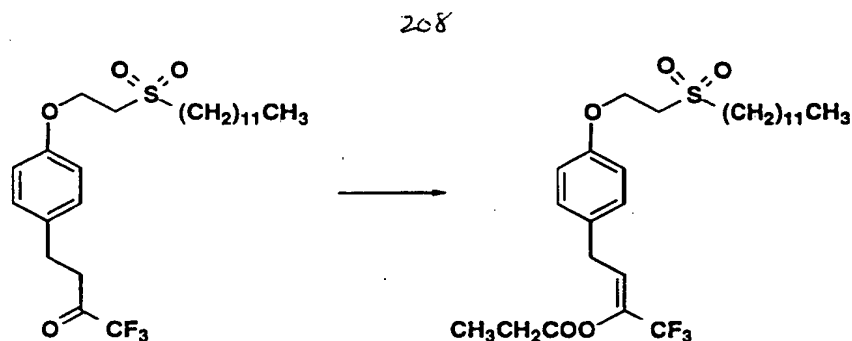


Reaction of 4-[4-[2-[bis(4-chlorophenyl)methoxy]ethylsulfonyl]ethoxy]phenyl]-1,1,1-trifluoro-2-butanone with acetic anhydride as described in example 260 gave the title material as an oil (85%).

Anal. Calcd. for $C_{29}H_{27}Cl_2F_3O_6S \cdot 0.5 H_2O$: C 54.38, H 4.41, S 5.01. Found: C 54.38, H 4.26, S 4.86.

15 **Example 263**

(Z)-4-[4-[2-(Dodecylsulfonyl)ethoxy]phenyl]-1,1,1-trifluoro-2-propionyloxy-2-butene.

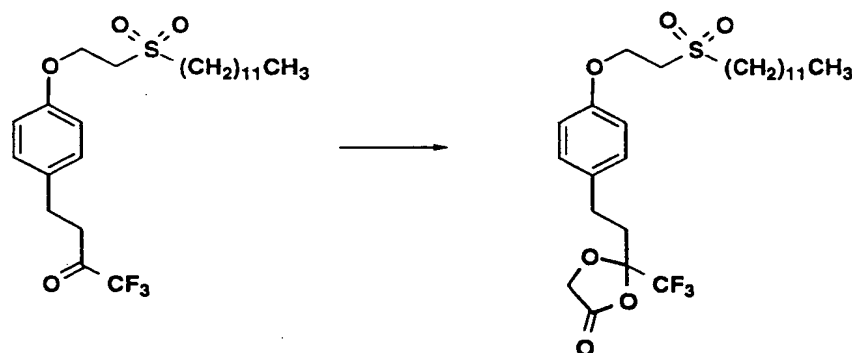


Reaction of 4-[4-[2-(dodecylsulfonyl)ethoxy]phenyl]-1,1,1-trifluoro-2-butanone (0.87 g, 1.82 mmol) with propionic anhydride using the procedure described above gave 0.866 g (89%) of the title material as a white solid: mp 60-63°C.

Anal. Calcd. for $C_{27}H_{41}F_3O_5S$: C 60.65, H 7.73, S 6.00. Found: C 60.51, H 7.83, S 6.01.

10 Example 264

4-[4-[2-(Dodecylsulfonyl)ethoxy]phenyl]-1,1,1-trifluoro-2-butanone, glycolic acid-ketal ester.



15

A solution of 4-[4-[2-(dodecylsulfonyl)ethoxy]phenyl]-1,1,1-trifluoro-2-butanone (0.80 g) in toluene (40 ml) was treated with glycolic acid (0.16 g) and p-toluene sulfonic acid (0.10 g) and the resulting mixture was heated

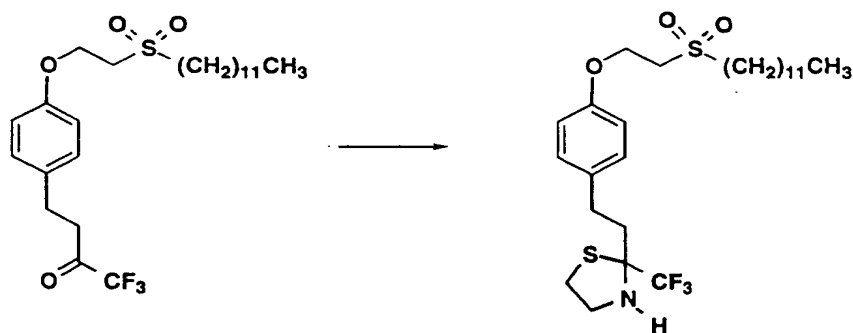
209

under reflux for 6 h. Additional quantities of glycolic acid (5×0.16 g) and p-toluenesulfonic acid (5×0.06 g) were added periodically after every hour of heating. The cooled reaction mixture was diluted with ethyl acetate, washed with saturated sodium bicarbonate and brine and dried over magnesium sulfate. Evaporation of the solvent under reduced pressure and chromatography of the residue on silica gel (elution toluene-ethyl acetate 8:2) gave 0.187 g (21%) of the title material as a white solid: mp 69-71°C.

Anal. Calcd. for $C_{26}H_{39}F_3O_6S$: C 58.19, H 7.33, S 5.97. Found: C 58.11, H 7.35, S 6.09.

Example 265

4-[4-[2-(Dodecylsulfonyl)ethoxy]phenyl]-1,1,1-trifluorobutanone,
thiazolidine derivative with 2-aminoethanethiol.



A solution of 4-[4-[2-(dodecylsulfonyl)ethoxy]phenyl]-1,1,1-trifluorobutanone (0.60 g, 1.25 mmol) in dry toluene (50 ml) was heated under reflux and then treated with 2-aminoethanethiol (3×0.20 g) added in three portions over 12 h. The reaction mixture was then washed with brine and dried over magnesium sulfate. Evaporation of the solvent in

210

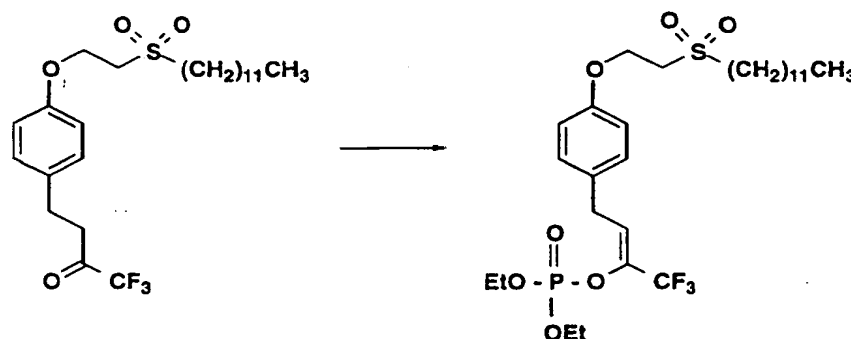
vacuo and chromatography of the residue on silica gel (elution toluene-ethyl acetate 85:15) gave 0.603 g (89%) of the title thiazolidine as a syrup. Anal. Calcd. for $C_{26}H_{42}F_3NO_3S_2$: C 58.07, H 7.87, N 2.60, S 11.93. Found: C 57.93, H 8.09, N 2.52, S 11.46.

5

Example 266

(Z)-4-[4-[2-(Dodecylsulfonyl)ethoxy]phenyl]-1,1,1-trifluoro-2-diethylphosphoryloxy-2-butene.

10



A solution of 4-[4-[2-(dodecylsulfonyl)ethoxy]phenyl]-1,1,1-trifluorobutanone (1.50 g, 3.13 mmol) in dry dichloromethane (40 ml) was cooled to 0°C and treated with triethylamine (0.87 ml) and 4-dimethylaminopyridine (0.77 g) then diethyl phosphorochloridate (1.35 ml) was added dropwise and the resulting mixture was stirred at 0°C for 2 h. The reaction mixture was then diluted with ethyl acetate, washed with sodium bicarbonate, brine and dried (magnesium sulfate). After evaporation of the solvent under reduced pressure, the residue was chromatographed on silica gel (elution toluene-ethyl acetate, 8:2) to give 1.539 g (80%) of the title enol phosphate as white crystals (hexane) : mp 33°C.

211

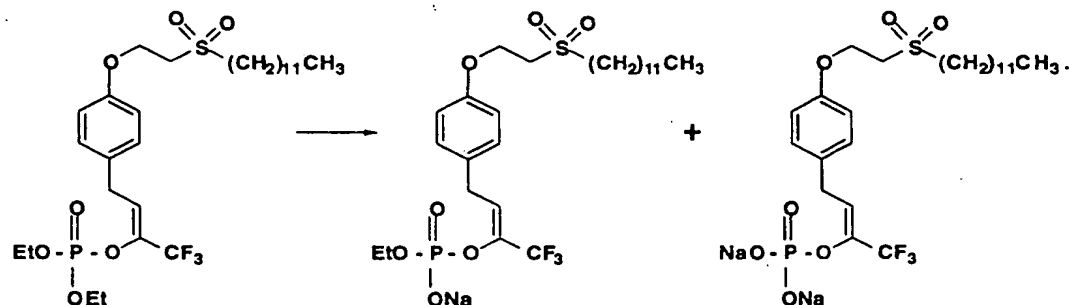
Anal. Calcd. for $C_{28}H_{46}F_3O_7PS$: C 54.71, H 7.54, S 5.22. Found: C 54.82, H 7.64, S 5.39.

Example 267

5

(Z)-4-[4-[2-(Dodecylsulfonyl)ethoxy]phenyl]-1,1,1-trifluoro-2-ethylphosphoryloxy-2-butene sodium salt and
(Z)-4-[4-[2-(Dodecylsulfonyl)ethoxy]phenyl]-1,1,1-trifluoro-2-phosphoryloxy-2-butene, disodium salt.

10



A solution of (Z)-4-[4-[2-(dodecylsulfonyl)ethoxy]phenyl]-1,1,1-trifluoro-2-diethylphosphoryloxy-2-butene (0.778 g, 1.27 mmol) in acetonitrile (20 ml) was treated with chlorotrimethylsilane (1.0 ml) and potassium iodide (0.63 g) and the resulting mixture was heated under reflux for 5 h. The cooled mixture was then treated with sodium bicarbonate (1 g) and water (5 ml) and stirred for 30 min. The solid was then removed by filtration and the filtrate was concentrated *in vacuo*. The residue was then purified on silica gel using a mixture of ethyl acetate, methanol and water (7:3:0 to 65:35:5) as eluent.

20

The first fractions gave the ethyl-phosphoryloxy sodium salt (0.210 g, 27%) as a white solid.

212

Anal. Calcd. for $C_{26}H_{41}F_3O_7PSNa \cdot 0.3 H_2O$: C 50.86, H 6.83, S 5.22. Found:

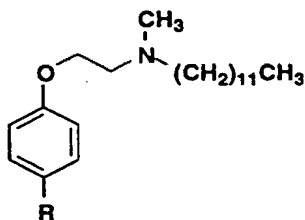
~~C 50.81, H 6.98, S 5.32.~~

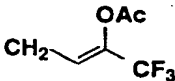
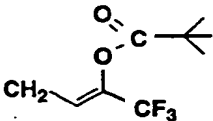
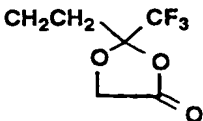
The tail fractions gave the phosphoryloxy disodium salt (0.259 g, 34%) as a white solid.

5 Anal. Calcd. for $C_{24}H_{36}F_3O_7PSNa_2 \cdot 0.3 H_2O$: C 43.90, H 6.45, S 4.88. Found: C 43.97, H 6.08, S 5.08.

10 The following prodrugs may be prepared by the general procedure described above.

Table: Pro-drugs (1)



Exp. No.	R	Analysis
268		<p>$C_{27}H_{42}F_3NO_3 \cdot HCl \cdot 0.5 H_2O$</p> <p>Calcd: C 61.06, H 8.35, N 2.64</p> <p>Found: C 60.76, H 7.83, N 2.70</p>
269		<p>$C_{30}H_{48}F_3NO_3 \cdot HCl \cdot 0.5 H_2O$</p> <p>Calcd: C 62.87, H 8.79, N 2.44</p> <p>Found: C 62.91, H 8.98, N 2.52</p>
270		<p>$C_{27}H_{42}F_3NO_4 \cdot HCl$</p> <p>Calcd: C 60.27, H 8.05, N 2.60</p> <p>Found: C 60.15, H 7.52, N 2.62</p>

213

Table: Pro-drugs (2)

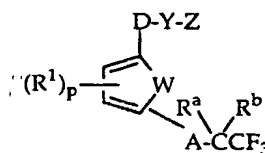
EXP. #	STRUCTURE	ANALYSIS
271		$C_{29}H_{27}Cl_2F_3O_6S.HCl. 0.5 H_2O$ Calcd: C 54.38, H 4.41, N 5.01 Found: C 54.38, H 4.26, N 4.86
272		$C_{31}H_{34}Cl_2F_3O_8PS$ Calcd: C 51.32, H 4.72, N 4.42 Found: C 51.39, H 4.54, N 4.61
273		$C_{32}H_{36}Cl_2F_3O_7PS. 0.8 H_2O$ Calcd: C 52.08, H 5.14 Found: C 51.92, H 4.79
274		$C_{28}H_{26}Cl_2F_3O_7PSNa_2$ Calcd for $(M - 2Na + H)^+ = 665$ Found: 665

214

CLAIMS

We claim:

1. A compound of the formula



- wherein W is CH=CH, CH=N, O or S;

R^1 is (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)alkoxy, (C₁-C₆)alkylthio, halo, hydroxy, cyano, $-\overset{\text{O}}{\underset{\text{||}}{\text{C}}}-\overset{\text{R}^2}{\underset{|}{\text{N}}}-\text{R}^3$ in which R² and R³ are each independently hydrogen or (C₁-C₆)alkyl, -COO-(C₁-C₆)alkyl, CF₃,

- (C₁-C₆)alkylphenyl, phenyl or phenyl substituted by one or more of (C₁-C₆)alkyl, -COO-(C₁-C₆)alkyl, $-\overset{\text{O}}{\underset{\text{||}}{\text{C}}}-\overset{\text{R}^2}{\underset{|}{\text{N}}}-\text{R}^3$ in which R² and R³ are as defined above, halo, hydroxy, -O-(C₁-C₆)alkyl, -S-(C₁-C₆)alkyl or (C₂-C₆)alkenyl;

- p is 0, 1 or 2;

A is V-(R^c)_n -;

R^c is a straight or branched chain alkyl group;


25

n is 0 or an integer of from 1 to 6;

2/5

R^a and R^b when taken together form an oxo group; or R^a and R^b are each independently hydrogen or OH;

V is O, -S-, -SO-, -SO₂-, -CONH or NHCO when n is an integer of from 1 to 6 or V is (C₂-C₆) alkenyl or a bond when n is 0 or an integer of from 1 to 6;

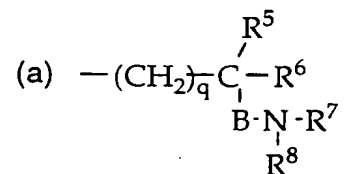
D is -(CH₂)_m or a bond linking the  ring to Y;

m is an integer of from 1 to 6;

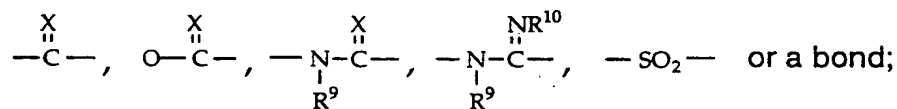
Y is -O-, -S-, -SO-, -SO₂-, $\overset{|}{\text{N-R}^4}$ or a bond;

R^4 is as defined below for R^7 ;

15 Z is:



in which B is:



X is S or O;

25 q is an integer from 1 to 6;

216

R⁹ is hydrogen or (C₁-C₆)alkyl;

R¹⁰ is hydrogen, CN, NO₂, OH, -O-(C₁-C₆)alkyl, (C₁-C₆)alkyl, phenyl or (C₁-C₆)alkylphenyl;

5

R⁵ and R⁶ are each independently hydrogen or (C₁-C₁₈) alkyl;

R⁷ and R⁸ are each independently;

10 (a) hydrogen;

(b) (C₁-C₁₈)alkyl;

(c) (C₁-C₁₈)alkyl substituted by one or more of

15

(1) phenyl;

(2) phenyl substituted by 1-5 fluoro, 1-3 halo (other than fluoro), 1-3(C₁-C₆)alkoxy, 1-3(C₁-C₆)alkyl, nitro, cyano, hydroxy, trifluoromethyl, (C₁-C₆)alkylthio, amino, 1-3 (C₁-C₆) alkylamino, di(C₁-C₆)alkylamino, -CO₂H, -COO-(C₁-C₆)alkyl, -SO₃H, -SO₂NHR¹⁵ in which R¹⁵ is hydrogen or (C₁-C₆)alkyl, or $\begin{matrix} \text{O} & \text{R}^2 \\ \parallel & | \\ -\text{C} & -\text{N}-\text{R}^3 \end{matrix}$ in which R² and R³ are as defined above;

25

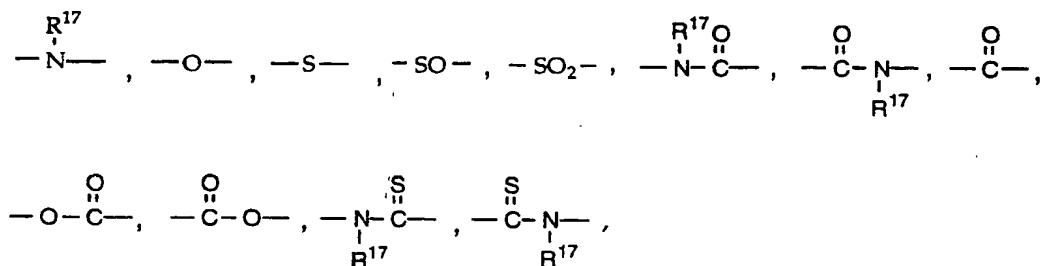
(3) heterocyclic selected from oxadiazolyl, isoxazolyl, oxazolyl, furyl and thiazolyl;

2/7

- (4) heterocyclic substituted by one or more of phenyl, phenyl substituted by 1-3 halo, (C₁-C₆)alkoxy, (C₁-C₆)alkyl, nitro, cyano, hydroxy, trifluoromethyl, (C₁-C₆) alkylthio, amino, (C₁-C₆) alkylamino, di(C₁-C₆) alkylamino, CO₂H, -COO-(C₁-C₆) alkyl, -SO₃H, SO₂NHR¹⁵ in which R¹⁵ is hydrogen or (C₁-C₆) alkyl, or $-\overset{\text{O}}{\overset{\parallel}{\text{C}}}-\overset{\text{R}^2}{\underset{|}{\text{N}}}-\text{R}^3$ in which R² and R³ are as defined above, (C₁-C₆) alkyl or (C₁-C₆) alkyl substituted by one or more phenyl or heterocyclic groups, said phenyl or heterocyclic group being unsubstituted or substituted by 1-3 halo, 1-3 (C₁-C₆) alkoxy, 1-3 (C₁-C₆) alkyl, nitro, cyano, hydroxy, trifluoromethyl, (C₁-C₆) alkylthio, amino, 1-3 (C₁-C₆) alkylamino, di(C₁-C₆) alkylamino, COOH, -COO-(C₁-C₆) alkyl, -SO₃H, -SO₂NHR¹⁵ in which R¹⁵ is hydrogen or (C₁-C₆) alkyl, or $-\overset{\text{O}}{\overset{\parallel}{\text{C}}}-\overset{\text{R}^2}{\underset{|}{\text{N}}}-\text{R}^3$ in which R² and R³ are each independently hydrogen or (C₁-C₆) alkyl, the heterocyclic radical being selected from imidazolyl, oxadiazolyl, isoxazolyl, pyrrolyl, pyrazolyl, oxazolyl, furyl, thianyl or thiazolyl;
- (5) carboxy or -COO-(C₁-C₆) alkyl;
- (6) hydroxy, halo, -O-(C₁-C₆) alkyl or -S-(C₁-C₆) alkyl, with the proviso that the OH, ethers or thioethers cannot be on the carbon bearing the heteroatoms;
- (7) cyano;

218

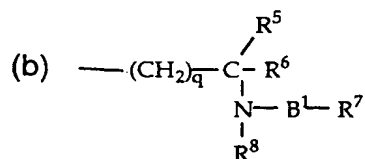
(8) halogen, trifluoromethyl or trifluoroacetyl;

(9) $\text{CH}_2 \text{L-R}^{16}$ in which L is

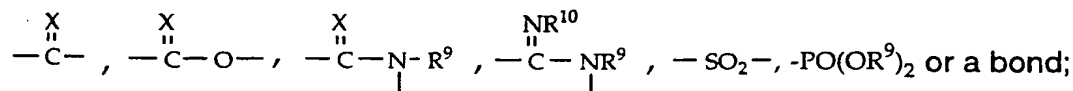
5

or $-\text{O-SiR}^{16}\text{R}^{18}\text{R}^{19}$ or a bond in which R^{16} and R^{17} are each independently (C1-C18)alkyl or (C2-C18)alkenyl or (C1-C18)alkyl or (C2-C18)alkenyl substituted by one or more phenyl or heterocyclic radicals, said phenyl or heterocyclic radicals being unsubstituted or substituted by 1-5 fluoro, 1-3 halo (other than fluoro), 1-3 (C1-C6)alkoxy, 1-3(C1-C6)alkyl, nitro, cyano, hydroxy, 1-3 trifluoromethyl, 1-3 (C1-C6)alkylthio, amino, 1-3(C1-C6)alkylamino, 1-3 di(C1-C6)alkylamino, CO_2H , 1-3 $-\text{COO}(\text{C1-C6})\text{alkyl}$, $-\overset{\text{O}}{\parallel}\text{C}-\underset{\text{R}^3}{\underset{|}{\text{N}}}-\overset{\text{R}^2}{\overset{|}{\text{C}}}$ or $-\text{SO}_2\text{NHR}^9$ in which R^9 is hydrogen or (C1-C6)alkyl and R^2 and R^3 are as defined above;

15

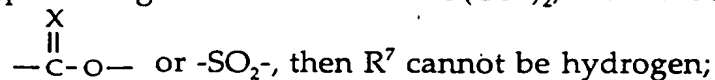
in which B^1 is

20



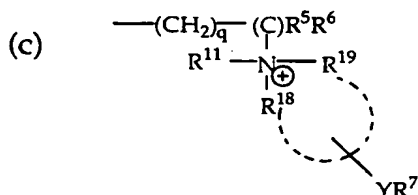
219

providing that when B^1 is $-PO(OR^9)$, then R^7 becomes R^9 , and when B^1 is



X, q, R⁵, R⁶, R⁷, R⁸, R⁹ and R¹⁰ are as defined in (a);

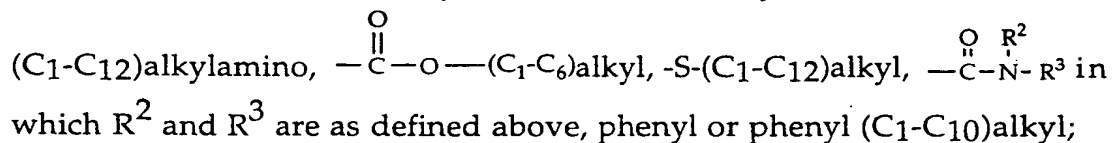
5



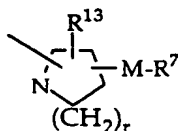
in which q , R^5 and R^6 are as defined above;

10 R^{18} , R^{19} and R^{11} are as defined below for R^7 and R^8 except that they may not be hydrogen, or R^{18} and R^{19} taken together with the nitrogen to which they are attached represent a 4, 5- or 6-membered heterocyclic ring and Y, R^7 and R^{11} are as defined above, or R^{18} , R^{19} and R^{11} taken together with the nitrogen to which they are attached represent

15 pyridinium, said pyridinium group being unsubstituted or substituted by
(C₁-C₁₂)alkyl, (C₁-C₁₂)alkoxy, amino, (C₁-C₁₂)alkylamino, di



20 d)



220

in which R^{13} is (C₁-C₁₈)alkyl or (C₁-C₁₈)alkyl substituted by carboxy,

$-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{O}-(\text{C}_1-\text{C}_{12})$ alkyl, $-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{N}-R^3$ in which R^2 and R^3 are as defined above,

hydroxy, $-\text{O}-(\text{C}_1-\text{C}_6)$ alkyl or $-\text{S}-(\text{C}_1-\text{C}_6)$ alkyl substituted by 1 or 2 phenyl or substituted phenyl groups, the substituents for the substituted phenyl

- 5 groups being 1-5 fluoro or 1-3 halo (other than fluoro), (C₁-C₆) alkoxy, (C₁-C₆) alkyl, nitro, cyano, hydroxy, trifluoromethyl, (C₁-C₆) alkylthio, amino, (C₁-C₆) alkylamino, di(C₁-C₆) alkylamino, CO₂H, COO-(C₁-C₆) alkyl, SO₃H, SO₂NHR¹⁵ in which R^{15} is hydrogen or (C₁-C₆) alkyl or $-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{N}-R^3$ in which R^2 and R^3 are as defined above;

10

r is 0 or an integer of from 1 to 3;

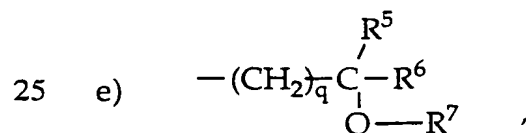
R^7 is as defined above;

- 15 M is $-(\text{CH}_2)_m\text{T}$ where T is $-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-$, $-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{O}$, $-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{N}-$, in which R^2 is as defined above, $-\text{SO}_2-$ or a bond when MR^7 is on nitrogen and providing that when T is $-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-$ or $-\text{SO}-$ or $-\text{SO}_2-$, then R^7 cannot be hydrogen, and T is $-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-$, $-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{O}-$, $-\text{O}-$, $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$, $-\overset{\text{R}^{14}}{\underset{\text{R}^{14}}{\text{N}}}-$ or a bond when MR^7 is on a carbon atom of the heterocyclic ring;

20

R^{14} is hydrogen or (C₁-C₆)alkyl;

m is 0 or an integer of 1-6;



221

wherein Q is -O-, -S-, -SO- or -SO₂-, and q, R⁵, R⁶ and R⁷ are as defined above, providing that when Q is -SO- or -SO₂-, R⁷ cannot be hydrogen;

- f) R⁷ wherein R⁷ is defined above, providing that when Y is -SO- or -SO₂-, R⁷ cannot be hydrogen; and

R¹⁸ and R¹⁹ are phenyl or phenyl substituted by 1-3 halo, (C₁-C₆) alkoxy, (C₁-C₆) alkyl, nitro, cyano, hydroxy, trifluoromethyl, (C₁-C₆) alkylthio, amino, (C₁-C₆) alkylamino, di(C₁-C₆) alkylamino, CO₂H, -COO-(C₁-C₆) alkyl, -SO₃H, SO₂NHR¹⁵ in which R¹⁵ is hydrogen or (C₁-C₆) alkyl, or $\begin{array}{c} \text{O} \quad \text{R}^2 \\ \parallel \quad | \\ -\text{C}-\text{N}-\text{R}^3 \end{array}$ in which R² and R³ are as defined above; or a pharmaceutically acceptable salt, solvate or prodrug thereof.

2. A compound of claim 1 wherein W is CH=CH, D is a bond linking Y to the ring and Y is -O-.

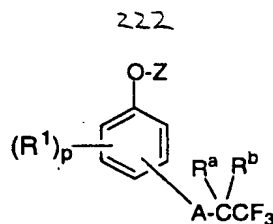
3. A compound of claim 2 wherein R¹ is benzyl; p is 0, 1 or 2; A is V -(CH₂)_n- wherein V is (C₂-C₆) alkenyl or a bond; and n is 0 or an integer of from 1 to 6.

20

4. A compound of claim 3 wherein A is -(CH₂)_n; n is 0 or an integer of from 1 to 6; and the group -(CH₂)_n-COCF₃ is in the meta or para position of the phenyl ring.

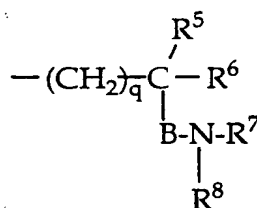
5. A compound of the formula

25

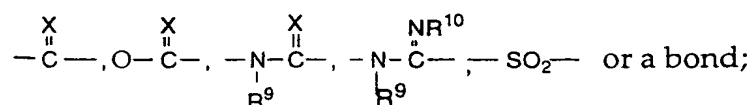


- wherein R^1 is benzyl; p is 0, 1 or 2; A is $V-(CH_2)_n$; V is
 (C₂-C₆) alkenyl or a bond; n is 0 or an integer of from 1 to 6; R^a and R^b
 5 when taken together form an oxo group, or R^a and R^b are each
 independently hydrogen or OH; and Z is

(a)



10

in which B is

- 15 X is S or O;

q is an integer of from 1 to 6;

R^9 is hydrogen or (C₁-C₆) alkyl;

20

R^{10} is hydrogen, CN, NO₂, OH, -O-(C₁-C₆) alkyl, (C₁-C₆) alkyl, phenyl or
 (C₁-C₆) alkylphenyl;

R⁵ and R⁶ are each independently hydrogen or (C₁-C₆) alkyl; and R⁷ and R⁸ are each independently

- a) hydrogen;
- b) (C₁-C₁₈) alkyl;
- 5 c) (C₁-C₁₈) alkyl substituted by one or more of
 - (1) phenyl;
 - (2) phenyl substituted by 1-5 fluoro, 1-3 halo (other than fluoro), 1-3 (C₁-C₆) alkoxy, 1-3 (C₁-C₆) alkyl, nitro, cyano, hydroxy, trifluoromethyl, (C₁-C₆) alkylthio, amino, 1-3 (C₁-C₆) alkylamino,

10 di(C₁-C₆) alkylamino, -CO₂H, -COO-(C₁-C₆) alkyl; -SO₃H, -SO₂NHR¹⁵

in which R¹⁵ is hydrogen or (C₁-C₆) alkyl, or $\begin{array}{c} \text{O} \text{ R}^2 \\ \parallel \quad | \\ \text{C} - \text{N} - \text{R}^3 \end{array}$ in which R² and R³ are each independently hydrogen or (C₁-C₆) alkyl;

(3) heterocyclic selected from oxadiazolyl, isoxazolyl, oxazolyl, furyl and thiazolyl;

15 (4) heterocyclic substituted by one or more of phenyl, phenyl substituted by 1-3 halo, (C₁-C₆) alkoxy, (C₁-C₆) alkyl, nitro, cyano, hydroxy, trifluoromethyl, (C₁-C₆) alkylthio, amino, (C₁-C₆) alkylamino, di(C₁-C₆) alkylamino, CO₂H, -COO-(C₁-C₆) alkyl, -SO₃H,

20 SO₂NHR¹⁵ in which R¹⁵ is hydrogen or (C₁-C₆) alkyl, or $\begin{array}{c} \text{O} \text{ R}^2 \\ \parallel \quad | \\ \text{C} - \text{N} - \text{R}^3 \end{array}$

in which R² and R³ are as defined above, (C₁-C₆) alkyl or (C₁-C₆) alkyl substituted by one or more phenyl or heterocyclic groups, said phenyl or heterocyclic group being unsubstituted or substituted by 1-3 halo, 1-3 (C₁-C₆) alkoxy, 1-3 (C₁-C₆) alkyl, nitro, cyano, hydroxy, trifluoromethyl, (C₁-C₆) alkylthio, amino, 1-3 (C₁-C₆) alkylamino,

25 di(C₁-C₆) alkylamino, COOH, -COO-(C₁-C₆) alkyl, -SO₃H, -SO₂NHR¹⁵

in which R¹⁵ is hydrogen or (C₁-C₆) alkyl, or $\begin{array}{c} \text{O} \text{ R}^2 \\ \parallel \quad | \\ \text{C} - \text{N} - \text{R}^3 \end{array}$ in which R² and R³ are each independently hydrogen or (C₁-C₆) alkyl, the

224

heterocyclic radical being selected from imidazolyl, oxadiazolyl, isoxazolyl, pyrrolyl, pyrazolyl, oxazolyl, furyl, thianyl or thiazolyl;

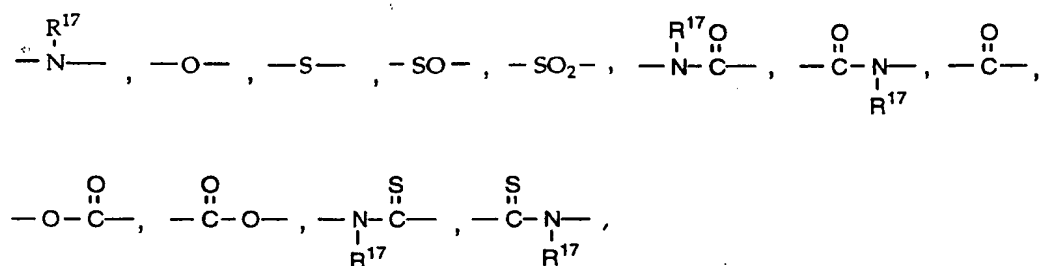
(5) carboxy or $\text{-COO-(C}_1\text{-C}_6\text{) alkyl}$;

(6) hydroxy, halo, $\text{-O-(C}_1\text{-C}_6\text{) alkyl}$ or $\text{-S(C}_1\text{-C}_6\text{) alkyl}$, with the proviso that the OH, ethers or thioethers cannot be on the carbon bearing the heteroatoms;

(7) cyano;

(8) halogen, trifluoromethyl or trifluoroacetyl; or

(9) $\text{CH}_2\text{ L-R}^{16}$ in which L is



or $\text{-O-SiR}^{16}\text{R}^{18}\text{R}^{19}$ or a bond in which R^{16} and R^{17} are each independently $(\text{C}_1\text{-C}_{18})$ alkyl or $(\text{C}_2\text{-C}_{18})$ alkenyl or $(\text{C}_1\text{-C}_{18})$ alkyl or $(\text{C}_2\text{-C}_{18})$ alkenyl substituted by one or more phenyl or heterocyclic radicals, said phenyl or heterocyclic radicals being unsubstituted or substituted by 1-5 fluoro, 1-3 halo (other than fluoro), 1-3 $(\text{C}_1\text{-C}_6)$ alkoxy, 1-3 $(\text{C}_1\text{-C}_6)$ alkyl, nitro, cyano, hydroxy, 1-3 trifluoromethyl, 1-3 $(\text{C}_1\text{-C}_6)$ alkylthio, amino, 1-3

$(\text{C}_1\text{-C}_6)$ alkylamino, 1-3 di $(\text{C}_1\text{-C}_6)$ alkylamino, CO_2H , 1-3 -COO

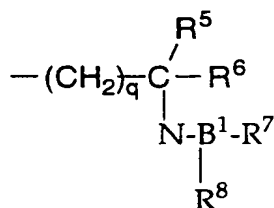
$(\text{C}_1\text{-C}_6)$ alkyl, $\begin{array}{c} \text{O} \text{ R}^2 \\ || \quad | \\ \text{---C---N---} \end{array} \text{R}^3$ or $\text{-SO}_2\text{NHR}^9$ in which R^9 is hydrogen or $(\text{C}_1\text{-C}_6)$ alkyl and R^2 and R^3 are as defined above; and R^{18} and R^{19} are phenyl or phenyl substituted by 1-3 halo, $(\text{C}_1\text{-C}_6)$ alkoxy,

225-

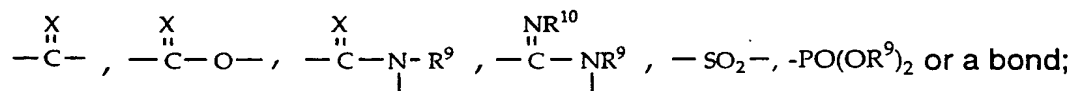
(C₁-C₆) alkyl, nitro, cyano, hydroxy, trifluoromethyl, (C₁-C₆) alkylthio, amino, (C₁-C₆) alkylamino, di(C₁-C₆) alkylamino, CO₂H, -COO-(C₁-C₆) alkyl, -SO₃H, SO₂NHR¹⁵ in which R¹⁵ is hydrogen or (C₁-C₆) alkyl, or $-\overset{\text{O}}{\underset{\text{R}^2}{\underset{|}{\text{C}}}}-\text{N}-\text{R}^3$ in which R² and R³ are as defined above;

5

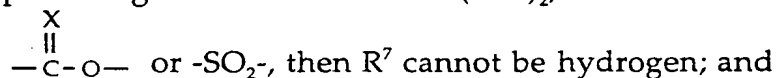
(b)



10 in which B^1 is



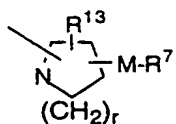
providing that when B¹ is -PO(OR⁹)₂, then R⁷ becomes R⁹, and when B¹ is



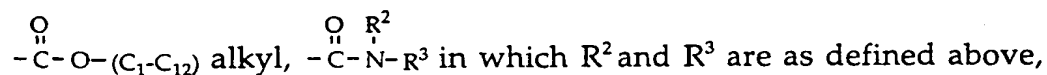
15

$X, q, R^5, R^6, R^7, R^8, R^9$ and R^{10} are as defined above in (a);

(c)



20 in which R¹³ is (C₁-C₁₈)alkyl or (C₁-C₁₈)alkyl substituted by carboxy,

hydroxy, -O-(C₁-C₆) alkyl or -S-(C₁-C₆) alkyl substituted by 1 or 2 phenyl or

226

- substituted phenyl groups, the substituents for the substituted phenyl groups being 1-5 fluoro or 1-3 halo (other than fluoro), (C₁-C₆) alkoxy, (C₁-C₆) alkyl, nitro, cyano, hydroxy, trifluoromethyl, (C₁-C₆) alkylthio, amino, (C₁-C₆) alkylamino, di(C₁-C₆) alkylamino, CO₂H, COO-(C₁-C₆) alkyl, SO₃H, SO₂NHR¹⁵ in which R¹⁵ is hydrogen or (C₁-C₆) alkyl or $-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\overset{\text{R}^2}{\text{N}}-\text{R}^3$ in which R² and R³ are as defined above;

r is 0 or an integer of from 1 to 3;

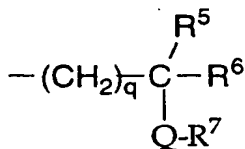
- 10 R⁷ is as defined above;

- M is -(CH₂)_mT where T is $-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-$, $-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{O}-$, $-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\overset{\text{R}^2}{\text{N}}-$, in which R² is as defined above, -SO₂- or a bond when MR⁷ is on nitrogen and providing that when T is $-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-$ or -SO- or -SO₂-, then R⁷ cannot be hydrogen, and T
- 15 is $-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-$, $-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{O}-$, -O-, -S-, -SO-, -SO₂-, $-\overset{\text{R}^{14}}{\text{N}}-$ or a bond when MR⁷ is on a carbon atom of the heterocyclic ring;

R¹⁴ is hydrogen or (C₁-C₆)alkyl;

- 20 m is 0 or an integer of 1-6;

(d)

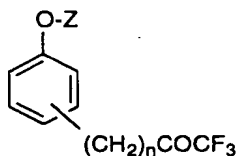


227

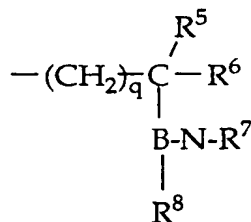
wherein Q is -O-, -S-, -SO-, or -SO₂- and q, R⁵, R⁶ and R⁷ are as defined above, providing that when Q is -SO- or -SO₂-, R⁷ cannot be hydrogen; or

- (e) R⁷ where R⁷ is as defined above, providing that when Y is -SO- or -SO₂-, R⁷ cannot be hydrogen; or a pharmaceutically acceptable salt, solvate or prodrug thereof.

6. A compound of the formula



wherein n is 0 or an integer of from 1 to 6, the substituent -(CH₂)_nCOCF₃ is in the meta or para position of the phenyl ring and Z is



in which B is $\text{—}\overset{\text{X}}{\underset{\text{||}}{\text{C}}}\text{—}$ or a bond; X is S or O; q is an integer of from 1 to 6; R⁵ and R⁶ are each independently hydrogen or (C₁-C₁₈) alkyl; and R⁷ and R⁸ are each independently

(a) hydrogen;

(b) (C₁-C₁₈)alkyl;

228

(c) (C₁-C₁₈)alkyl substituted by one or more of

(1) phenyl;

5 (2) phenyl substituted by 1-5 fluoro, 1-3 halo (other than fluoro),
1-3 (C₁-C₆) alkoxy, 1-3 (C₁-C₆) alkyl, nitro, cyano, hydroxy,
trifluoromethyl, (C₁-C₆) alkylthio, amino, 1-3 (C₁-C₆)
alkylamino, di(C₁-C₆) alkylamino, -CO₂H, -COO-(C₁-C₆) alkyl;
-SO₃H, -SO₂NHR¹⁵ in which R¹⁵ is hydrogen or (C₁-C₆) alkyl,
10 or $\begin{array}{c} \text{O} \quad \text{R}^2 \\ \parallel \quad | \\ -\text{C}-\text{N}-\text{R}^3 \end{array}$ in which R² and R³ are each independently
hydrogen or (C₁-C₆) alkyl;

(3) heterocyclic selected from oxadiazolyl, isoxazolyl, oxazolyl,
furyl and thiazolyl;

15

(4) heterocyclic substituted by one or more of phenyl, phenyl
substituted by 1-3 halo, (C₁-C₆)alkoxy, (C₁-C₆)alkyl,
nitro, cyano, hydroxy, trifluoromethyl, (C₁-C₆) alkylthio,
amino, (C₁-C₆) alkylamino, di(C₁-C₆) alkylamino, CO₂H,
20 -COO-(C₁-C₆) alkyl, -SO₃H, SO₂NHR¹⁵ in which R¹⁵ is
hydrogen or (C₁-C₆) alkyl, or $\begin{array}{c} \text{O} \quad \text{R}^2 \\ \parallel \quad | \\ -\text{C}-\text{N}-\text{R}^3 \end{array}$ in which R² and R³
are as defined above, (C₁-C₆) alkyl or (C₁-C₆) alkyl
substituted by one or more phenyl or heterocyclic groups,
said phenyl or heterocyclic group being unsubstituted or
substituted by 1-3 halo, 1-3 (C₁-C₆) alkoxy, 1-3 (C₁-C₆) alkyl,
25 nitro, cyano, hydroxy, trifluoromethyl, (C₁-C₆) alkylthio,
amino, 1-3 (C₁-C₆) alkylamino, di(C₁-C₆) alkylamino,

25

229

COOH, -COO-(C₁-C₆) alkyl, -SO₃H, -SO₂NHR¹⁵ in which
 R¹⁵ is hydrogen or (C₁-C₆) alkyl, or $-\overset{\overset{\text{O}}{\parallel}}{\text{C}}-\overset{\overset{\text{R}^2}{\mid}}{\text{N}}-\text{R}^3$ in which R²
 and R³ are each independently hydrogen or (C₁-C₆) alkyl,
 the heterocyclic radical being selected from imidazolyl,
 5 oxadiazolyl, isoxazolyl, pyrrolyl, pyrazolyl, oxazolyl, furyl,
 thianyl or thiazolyl;

(5) carboxy or -COO-(C₁-C₆) alkyl;

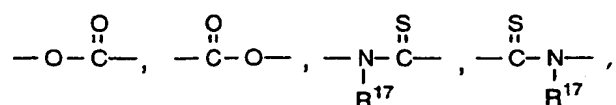
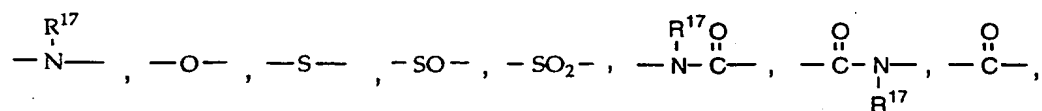
10 (6) hydroxy, halo, -O-(C₁-C₆) alkyl or -S-(C₁-C₆) alkyl, with the
 proviso that the OH, ethers or thioethers cannot be on the
 carbon bearing the heteroatoms;

(7) cyano;

15

(8) halogen, trifluoromethyl or trifluoroacetyl;

(9) CH₂ L-R¹⁶ in which L is



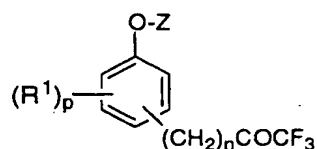
20

or -O-SiR¹⁶R¹⁸R¹⁹ or a bond in which R¹⁶ and R¹⁷ are each
 independently (C₁-C₁₈)alkyl or (C₂-C₁₈)alkenyl or (C₁-C₁₈)alkyl or

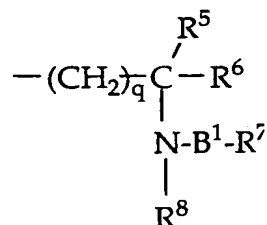
230

- (C₂-C₁₈)alkenyl substituted by one or more phenyl or heterocyclic radicals, said phenyl or heterocyclic radicals being unsubstituted or substituted by 1-5 fluoro, 1-3 halo (other than fluoro), 1-3 (C₁-C₆)alkoxy, 1-3(C₁-C₆)alkyl, nitro, cyano, hydroxy, 1-3 trifluoromethyl, 1-3 (C₁-C₆)alkylthio, amino, 1-3(C₁-C₆)alkylamino, 1-3 di(C₁-C₆)alkylamino, CO₂H, 1-3 -COO
- (C₁-C₆)alkyl, $\text{—}\overset{\text{O}}{\underset{\text{||}}{\text{C}}}\text{—}\overset{\text{R}^2}{\underset{|}{\text{N}}}\text{—R}^3$ or -SO₂NHR⁹ in which R⁹ is hydrogen or (C₁-C₆)alkyl and R² and R³ are as defined above; and R¹⁸ and R¹⁹ are phenyl or phenyl substituted by 1-3 halo, (C₁-C₆) alkoxy, (C₁-C₆) alkyl, nitro, cyano, hydroxy, trifluoromethyl, (C₁-C₆) alkylthio, amino, (C₁-C₆) alkylamino, di(C₁-C₆) alkylamino, CO₂H, -COO-(C₁-C₆) alkyl, -SO₃H, SO₂NHR¹⁵ in which R¹⁵ is hydrogen or (C₁-C₆) alkyl, or $\text{—}\overset{\text{O}}{\underset{\text{||}}{\text{C}}}\text{—}\overset{\text{R}^2}{\underset{|}{\text{N}}}\text{—R}^3$ in which R² and R³ are as defined above; or a pharmaceutically acceptable salt, solvate or prodrug thereof.

7. A compound of the formula

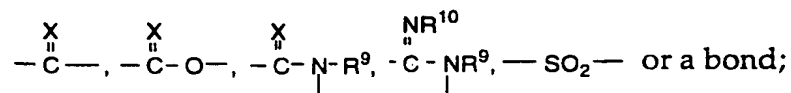


- in which R¹ is benzyl; p is 0, 1 or 2; n is 0 or an integer of from 1 to 6; the substituent -(CH₂)_nCOCF₃ is in the meta or para position of the phenyl ring; and Z is



231

in which B¹ is



5

q is an integer of from 1 to 6;

X is S or O;

10 R⁵ and R⁶ are each independently hydrogen or (C₁-C₁₈) alkyl;

R⁹ is hydrogen or (C₁-C₆) alkyl;

R¹⁰ is hydrogen, CN, NO₂, OH, -O-(C₁-C₆) alkyl or (C₁-C₆) alkyl; and R⁷

15 and R⁸ are each independently

(a) hydrogen;

(b) (C₁-C₁₈)alkyl;

20

(c) (C₁-C₁₈)alkyl substituted by one or more of

(1) phenyl;

25

(2) phenyl substituted by 1-5 fluoro, 1-3 halo (other than fluoro),
1-3 (C₁-C₆) alkoxy, 1-3 (C₁-C₆) alkyl, nitro, cyano, hydroxy,
trifluoromethyl, (C₁-C₆) alkylthio, amino, 1-3 (C₁-C₆)

232

alkylamino, di(C₁-C₆) alkylamino, -CO₂H, -COO-(C₁-C₆) alkyl;
 -SO₃H, -SO₂NHR¹⁵ in which R¹⁵ is hydrogen or (C₁-C₆) alkyl,
 or $\begin{array}{c} \text{O} \text{ R}^2 \\ \parallel \quad | \\ -\text{C}-\text{N}-\text{R}^3 \end{array}$ in which R² and R³ are each independently
 hydrogen or (C₁-C₆) alkyl;

5

(3) heterocyclic selected from oxadiazolyl, isoxazolyl, oxazolyl,
 furyl and thiazolyl;

10

(4) heterocyclic substituted by one or more of phenyl, phenyl
 substituted by 1-3 halo, (C₁-C₆)alkoxy, (C₁-C₆)alkyl,
 nitro, cyano, hydroxy, trifluoromethyl, (C₁-C₆) alkylthio,
 amino, (C₁-C₆) alkylamino, di(C₁-C₆) alkylamino, CO₂H,
 -COO-(C₁-C₆) alkyl, -SO₃H, SO₂NHR¹⁵ in which R¹⁵ is
 hydrogen or (C₁-C₆) alkyl, or $\begin{array}{c} \text{O} \text{ R}^2 \\ \parallel \quad | \\ -\text{C}-\text{N}-\text{R}^3 \end{array}$ in which R² and R³
 are as defined above, (C₁-C₆) alkyl or (C₁-C₆) alkyl

15

substituted by one or more phenyl or heterocyclic groups,
 said phenyl or heterocyclic group being unsubstituted or
 substituted by 1-3 halo, 1-3 (C₁-C₆) alkoxy, 1-3 (C₁-C₆) alkyl,
 nitro, cyano, hydroxy, trifluoromethyl, (C₁-C₆) alkylthio,
 amino, 1-3 (C₁-C₆) alkylamino, di(C₁-C₆) alkylamino,
 COOH, -COO-(C₁-C₆) alkyl, -SO₃H, -SO₂NHR¹⁵ in which
 R¹⁵ is hydrogen or (C₁-C₆) alkyl, or $\begin{array}{c} \text{O} \text{ R}^2 \\ \parallel \quad | \\ -\text{C}-\text{N}-\text{R}^3 \end{array}$ in which R²
 and R³ are each independently hydrogen or (C₁-C₆) alkyl,
 the heterocyclic radical being selected from imidazolyl,
 oxadiazolyl, isoxazolyl, pyrrolyl, pyrazolyl, oxazolyl, furyl,
 thianyl or thiazolyl;

25

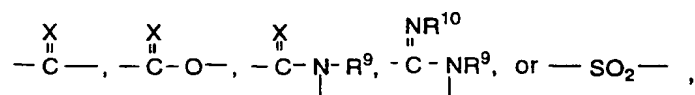
233

- (5) carboxy or $-\text{COO}-(\text{C}_1-\text{C}_6)$ alkyl;
- (6) hydroxy, halo, $-\text{O}-(\text{C}_1-\text{C}_6)$ alkyl or $-\text{S}-(\text{C}_1-\text{C}_6)$ alkyl, with the proviso that the OH, ethers or thioethers cannot be on the carbon bearing the heteroatoms;
- (7) cyano;
- (8) halogen, trifluoromethyl or trifluoroacetyl;
- (9) $\text{CH}_2 \text{ L-R}^{16}$ in which L is
- $$\begin{array}{c} \text{R}^{17} \\ | \\ -\text{N}-, -\text{O}-, -\text{S}-, -\text{SO}-, -\text{SO}_2-, -\text{N}-\overset{\text{O}}{\parallel}-, -\overset{\text{O}}{\parallel}-\text{N}-, -\overset{\text{O}}{\parallel}-\text{C}-, \\ | \\ \text{R}^{17} \end{array}$$
- $$\begin{array}{c} \text{O} \quad \text{O} \quad \text{S} \quad \text{S} \\ \parallel \quad \parallel \quad \parallel \quad \parallel \\ -\text{O}-\text{C}-, -\text{C}-\text{O}-, -\text{N}-\text{C}-, -\text{C}-\text{N}-, \\ | \quad \quad | \\ \text{R}^{17} \quad \text{R}^{17} \end{array}$$
- or $-\text{O-SiR}^{16}\text{R}^{18}\text{R}^{19}$ or a bond in which R^{16} and R^{17} are each independently $(\text{C}_1-\text{C}_{18})$ alkyl or $(\text{C}_2-\text{C}_{18})$ alkenyl or $(\text{C}_1-\text{C}_{18})$ alkyl or $(\text{C}_2-\text{C}_{18})$ alkenyl substituted by one or more phenyl or heterocyclic radicals, said phenyl or heterocyclic radicals being unsubstituted or substituted by 1-5 fluoro, 1-3 halo (other than fluoro), 1-3 (C_1-C_6) alkoxy, 1-3 (C_1-C_6) alkyl, nitro, cyano, hydroxy, 1-3 trifluoromethyl, 1-3 (C_1-C_6) alkylthio, amino, 1-3 (C_1-C_6) alkylamino, 1-3 di (C_1-C_6) alkylamino, CO_2H , 1-3 $-\text{COO}$ (C_1-C_6) alkyl, $-\overset{\text{O}}{\parallel}-\overset{\text{R}^2}{\text{N}}-\text{R}^3$ or $-\text{SO}_2\text{NHR}^9$ in which R^9 is hydrogen or (C_1-C_6) alkyl and R^2 and R^3 are as defined above; and R^{18} and R^{19} are phenyl or phenyl substituted by 1-3 halo, (C_1-C_6) alkoxy, (C_1-C_6) alkyl, nitro,

234

- cyano, hydroxy, trifluoromethyl, (C₁-C₆) alkylthio, amino, (C₁-C₆) alkylamino, di(C₁-C₆) alkylamino, CO₂H, -COO-(C₁-C₆) alkyl, -SO₃H, SO₂NHR¹⁵ in which R¹⁵ is hydrogen or (C₁-C₆) alkyl, or $-\overset{\overset{\text{O}}{\parallel}}{\text{C}}-\overset{\overset{\text{R}^2}{\mid}}{\text{N}}-\text{R}^3$ in which R² and R³ are as defined above; or a pharmaceutically acceptable salt, solvate or prodrug thereof.

8. A compound according to claim 7 wherein the substituent -(CH₂)_nCOCF₃ is in the para position of the phenyl ring, R⁵ and R⁶ are both hydrogen, q is 1, 2 or 3, n is 2 or 3, B¹ is

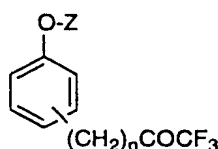


and R⁷ and R⁸ are each independently hydrogen or (C₁-C₁₈)alkyl.

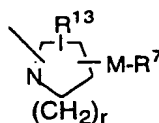
9. A compound according to claim 8 wherein q is 1, n is 2 and B¹ is $-\overset{\overset{\text{X}}{\parallel}}{\text{C}}-, -\overset{\overset{\text{X}}{\parallel}}{\text{C}}-\text{O}-, -\overset{\overset{\text{X}}{\parallel}}{\text{C}}-\underset{\underset{\mid}{\mid}}{\text{N}}-\text{R}^9, \text{ or } -\text{SO}_2-.$

15

10. A compound of the formula



- 20 wherein n is 0 or an integer of from 1 to 6; the substituent -(CH₂)_nCOCF₃ is in the meta or para position of the phenyl ring; and Z is



235

in which R^{13} is (C₁-C₁₈)alkyl or (C₁-C₁₈)alkyl substituted by carboxy,

$-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{O}-(\text{C}_1-\text{C}_{12})$ alkyl, $-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{N}-\overset{\text{R}^2}{\text{R}^3}$ in which R^2 and R^3 are each independently

hydrogen or (C₁-C₆) alkyl, hydroxy, -O-(C₁-C₆) alkyl or -S-(C₁-C₆) alkyl

substituted by 1 or 2 phenyl or substituted phenyl groups, the substituents

- 5 for the substituted phenyl groups being 1-5 fluoro or 1-3 halo (other than fluoro), (C₁-C₆) alkoxy, (C₁-C₆) alkyl, nitro, cyano, hydroxy, trifluoromethyl, (C₁-C₆) alkylthio, amino, (C₁-C₆) alkylamino, di(C₁-C₆) alkylamino, CO₂H, COO-(C₁-C₆) alkyl, SO₃H, SO₂NHR¹⁵ in which R^{15} is hydrogen or (C₁-C₆) alkyl or $-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{N}-\overset{\text{R}^2}{\text{R}^3}$ in which R^2 and R^3 are as defined above;

10

r is 0 or an integer of from 1 to 3;

R^7 is as defined below;

- 15 M is $-(\text{CH}_2)_m\text{T}$ where T is $-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-$, $-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{O}$, $-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\overset{\text{R}^2}{\text{N}}-$, in which R^2 is as defined above, -SO₂- or a bond when MR⁷ is on nitrogen and providing that when T is $-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-$ or -SO- or -SO₂-, then R^7 cannot be hydrogen, and T is $-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-$, $-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{O}-$, -O-, -S-, -SO-, -SO₂-, $-\overset{\text{R}^{14}}{\text{N}}-$ or a bond when MR⁷ is on a carbon atom of the heterocyclic ring;

20

R^{14} is hydrogen or (C₁-C₆)alkyl;

m is 0 or an integer of 1-6; and

25 R^7 is

(a) hydrogen;

(b) (C₁-C₁₈)alkyl;

(c) (C₁-C₁₈)alkyl substituted by one or more of

5

(1) phenyl;

10

(2) phenyl substituted by 1-5 fluoro, 1-3 halo (other than fluoro),
1-3 (C₁-C₆) alkoxy, 1-3 (C₁-C₆) alkyl, nitro, cyano, hydroxy,
trifluoromethyl, (C₁-C₆) alkylthio, amino, 1-3 (C₁-C₆)
alkylamino, di(C₁-C₆) alkylamino, -CO₂H, -COO-(C₁-C₆) alkyl;
-SO₃H, -SO₂NHR¹⁵ in which R¹⁵ is hydrogen or (C₁-C₆) alkyl,
or $\begin{array}{c} \text{O} \quad \text{R}^2 \\ \parallel \quad | \\ -\text{C}-\text{N}-\text{R}^3 \end{array}$ in which R² and R³ are each independently
hydrogen or (C₁-C₆) alkyl;

15

(3) heterocyclic selected from oxadiazolyl, isoxazolyl, oxazolyl,
furyl and thiazolyl;

20

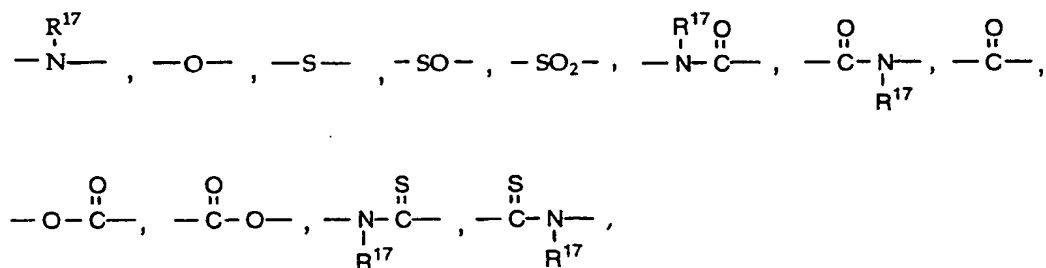
(4) heterocyclic substituted by one or more of phenyl, phenyl
substituted by 1-3 halo, (C₁-C₆)alkoxy, (C₁-C₆)alkyl,
nitro, cyano, hydroxy, trifluoromethyl, (C₁-C₆) alkylthio,
amino, (C₁-C₆) alkylamino, di(C₁-C₆) alkylamino, CO₂H,
-COO-(C₁-C₆) alkyl, -SO₃H, SO₂NHR¹⁵ in which R¹⁵ is
hydrogen or (C₁-C₆) alkyl, or $\begin{array}{c} \text{O} \quad \text{R}^2 \\ \parallel \quad | \\ -\text{C}-\text{N}-\text{R}^3 \end{array}$ in which R² and R³
are as defined above, (C₁-C₆) alkyl or (C₁-C₆) alkyl
substituted by one or more phenyl or heterocyclic groups,
said phenyl or heterocyclic group being unsubstituted or

25

237

substituted by 1-3 halo, 1-3 (C₁-C₆) alkoxy, 1-3 (C₁-C₆) alkyl, nitro, cyano, hydroxy, trifluoromethyl, (C₁-C₆) alkylthio, amino, 1-3 (C₁-C₆) alkylamino, di(C₁-C₆) alkylamino, COOH, -COO-(C₁-C₆) alkyl, -SO₃H, -SO₂NHR¹⁵ in which
 5 R¹⁵ is hydrogen or (C₁-C₆) alkyl, or $-\overset{\text{O}}{\underset{\text{R}^2}{\text{C}}}-\text{N}-\text{R}^3$ in which R² and R³ are each independently hydrogen or (C₁-C₆) alkyl, the heterocyclic radical being selected from imidazolyl, oxadiazolyl, isoxazolyl, pyrrolyl, pyrazolyl, oxazolyl, furyl, thianyl or thiazolyl;

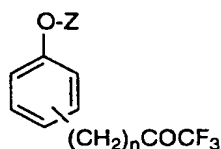
- 10 (5) carboxy or -COO-(C₁-C₆) alkyl;
- (6) hydroxy, halo, -O-(C₁-C₆) alkyl or -S-(C₁-C₆) alkyl, with the proviso that the OH, ethers or thioethers cannot be on the
 15 carbon bearing the heteroatoms;
- (7) cyano;
- (8) halogen, trifluoromethyl or trifluoroacetyl;
- 20 (9) CH₂ L-R¹⁶ in which L is



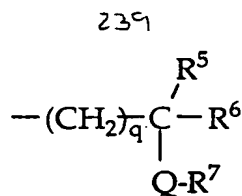
238

or $-\text{O}-\text{SiR}^{16}\text{R}^{18}\text{R}^{19}$ or a bond in which R^{16} and R^{17} are each independently $(\text{C}_1\text{-C}_{18})$ alkyl or $(\text{C}_2\text{-C}_{18})$ alkenyl or $(\text{C}_1\text{-C}_{18})$ alkyl or $(\text{C}_2\text{-C}_{18})$ alkenyl substituted by one or more phenyl or heterocyclic radicals, said phenyl or heterocyclic radicals being unsubstituted or substituted by 1-5 fluoro, 1-3 halo (other than fluoro), 1-3 $(\text{C}_1\text{-C}_6)$ alkoxy, 1-3 $(\text{C}_1\text{-C}_6)$ alkyl, nitro, cyano, hydroxy, 1-3 trifluoromethyl, 1-3 $(\text{C}_1\text{-C}_6)$ alkylthio, amino, 1-3 $(\text{C}_1\text{-C}_6)$ alkylamino, 1-3 di $(\text{C}_1\text{-C}_6)$ alkylamino, CO_2H , 1-3 $-\text{COO}$ $(\text{C}_1\text{-C}_6)$ alkyl, $-\overset{\text{O}}{\underset{\text{R}^2}{\text{C}}}-\text{N}-\text{R}^3$ or $-\text{SO}_2\text{NHR}^9$ in which R^9 is hydrogen or $(\text{C}_1\text{-C}_6)$ alkyl and R^2 and R^3 are as defined above; and R^{18} and R^{19} are phenyl or phenyl substituted by 1-3 halo, $(\text{C}_1\text{-C}_6)$ alkoxy, $(\text{C}_1\text{-C}_6)$ alkyl, nitro, cyano, hydroxy, trifluoromethyl, $(\text{C}_1\text{-C}_6)$ alkylthio, amino, $(\text{C}_1\text{-C}_6)$ alkylamino, di $(\text{C}_1\text{-C}_6)$ alkylamino, CO_2H , $-\text{COO}-(\text{C}_1\text{-C}_6)$ alkyl, $-\text{SO}_3\text{H}$, $\text{SO}_2\text{NHR}^{15}$ in which R^{15} is hydrogen or $(\text{C}_1\text{-C}_6)$ alkyl, or $-\overset{\text{O}}{\underset{\text{R}^2}{\text{C}}}-\text{N}-\text{R}^3$ in which R^2 and R^3 are as defined above; or a pharmaceutically acceptable salt, solvate or prodrug thereof.

11. A compound of the formula



in which n is 0 or an integer of from 1 to 6, the substituent $-(\text{CH}_2)_n\text{COCF}_3$ is in the meta or para position of the phenyl ring; and Z is



wherein q is an integer of from 1 to 6; R⁵ and R⁶ are each independently hydrogen or (C₁-C₁₈)alkyl;

5

Q is -O-, -S-, -SO-, or -SO₂-; and

R⁷ is

- (a) hydrogen;
- (b) (C₁-C₁₈)alkyl;
- (c) (C₁-C₁₈)alkyl substituted by one or more of
 - (1) phenyl;
 - (2) phenyl substituted by 1-5 fluoro, 1-3 halo (other than fluoro), 1-3 (C₁-C₆) alkoxy, 1-3 (C₁-C₆) alkyl, nitro, cyano, hydroxy, trifluoromethyl, (C₁-C₆) alkylthio, amino, 1-3 (C₁-C₆) alkylamino, di(C₁-C₆) alkylamino, -CO₂H, -COO-(C₁-C₆) alkyl; -SO₃H, -SO₂NHR¹⁵ in which R¹⁵ is hydrogen or (C₁-C₆) alkyl, or $\begin{array}{c} \text{O} \quad \text{R}^2 \\ \parallel \quad | \\ \text{---C---N---R}^3 \end{array}$ in which R² and R³ are each independently hydrogen or (C₁-C₆) alkyl;
 - (3) heterocyclic selected from oxadiazolyl, isoxazolyl, oxazolyl, furyl and thiazolyl;

25

240

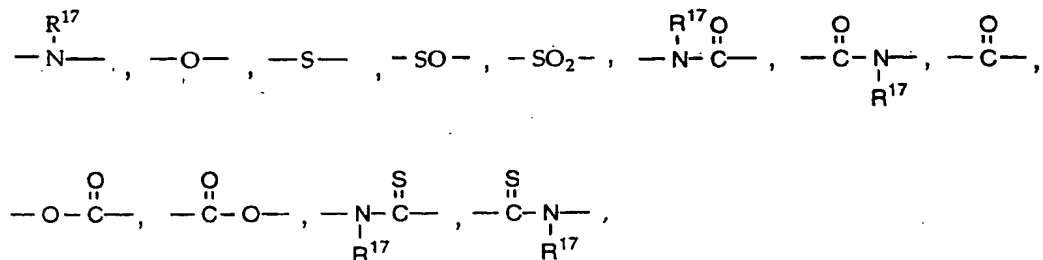
- (4) heterocyclic substituted by one or more of phenyl, phenyl substituted by 1-3 halo, (C₁-C₆)alkoxy, (C₁-C₆)alkyl, nitro, cyano, hydroxy, trifluoromethyl, (C₁-C₆) alkylthio, amino, (C₁-C₆) alkylamino, di(C₁-C₆) alkylamino, CO₂H, -COO-(C₁-C₆) alkyl, -SO₃H, SO₂NHR¹⁵ in which R¹⁵ is hydrogen or (C₁-C₆) alkyl, or $-\overset{\text{O}}{\overset{\parallel}{\text{C}}}-\overset{\text{R}^2}{\underset{|}{\text{N}}}-\text{R}^3$ in which R² and R³ are as defined above, (C₁-C₆) alkyl or (C₁-C₆) alkyl substituted by one or more phenyl or heterocyclic groups, said phenyl or heterocyclic group being unsubstituted or substituted by 1-3 halo, 1-3 (C₁-C₆) alkoxy, 1-3 (C₁-C₆) alkyl, nitro, cyano, hydroxy, trifluoromethyl, (C₁-C₆) alkylthio, amino, 1-3 (C₁-C₆) alkylamino, di(C₁-C₆) alkylamino, COOH, -COO-(C₁-C₆) alkyl, -SO₃H, -SO₂NHR¹⁵ in which R¹⁵ is hydrogen or (C₁-C₆) alkyl, or $-\overset{\text{O}}{\overset{\parallel}{\text{C}}}-\overset{\text{R}^2}{\underset{|}{\text{N}}}-\text{R}^3$ in which R² and R³ are each independently hydrogen or (C₁-C₆) alkyl, the heterocyclic radical being selected from imidazolyl, oxadiazolyl, isoxazolyl, pyrrolyl, pyrazolyl, oxazolyl, furyl, thianyl or thiazolyl;
- (5) carboxy or -COO-(C₁-C₆) alkyl;
- (6) hydroxy, halo, -O-(C₁-C₆) alkyl or -S-(C₁-C₆) alkyl, with the proviso that the OH, ethers or thioethers cannot be on the carbon bearing the heteroatoms;
- (7) cyano;

241

---(8)---halogen, trifluoromethyl or trifluoroacetyl;

(9) $\text{CH}_2 \text{L-R}^{16}$ in which L is

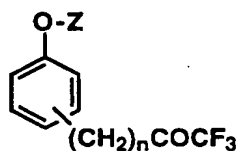
5



or $-\text{O-SiR}^{16}\text{R}^{18}\text{R}^{19}$ or a bond in which R^{16} and R^{17} are each independently (C₁-C₁₈)alkyl or (C₂-C₁₈)alkenyl or (C₁-C₁₈)alkyl or (C₂-C₁₈)alkenyl substituted by one or more phenyl or heterocyclic radicals, said phenyl or heterocyclic radicals being unsubstituted or substituted by 1-5 fluoro, 1-3 halo (other than fluoro), 1-3 (C₁-C₆)alkoxy, 1-3(C₁-C₆)alkyl, nitro, cyano, hydroxy, 1-3 trifluoromethyl, 1-3 (C₁-C₆)alkylthio, amino, 1-3 (C₁-C₆)alkylamino, 1-3 di(C₁-C₆)alkylamino, CO₂H, 1-3 -COO (C₁-C₆)alkyl, $-\overset{\text{O}}{\parallel}\text{C}-\underset{\text{R}^2}{\underset{|}{\text{N}}}-\text{R}^3$ or -SO₂NHR⁹ in which R⁹ is hydrogen or (C₁-C₆)alkyl and R² and R³ are as defined above; and R¹⁸ and R¹⁹ are phenyl or phenyl substituted by 1-3 halo, (C₁-C₆) alkoxy, (C₁-C₆) alkyl, nitro, cyano, hydroxy, trifluoromethyl, (C₁-C₆) alkylthio, amino, (C₁-C₆) alkylamino, di(C₁-C₆) alkylamino, CO₂H, -COO-(C₁-C₆) alkyl, -SO₃H, SO₂NHR¹⁵ in which R¹⁵ is hydrogen or (C₁-C₆) alkyl, or $-\overset{\text{O}}{\parallel}\text{C}-\underset{\text{R}^2}{\underset{|}{\text{N}}}-\text{R}^3$ in which R² and R³ are as defined above; or a pharmaceutically acceptable salt, solvate or prodrug thereof.

242

12. A compound of the formula



5 in which n is 0 or an integer of from 1 to 6; the substituent
 -(CH₂)_nCOCF₃ is in the meta or para position of the phenyl ring; and Z is

(a) hydrogen;

10 (b) (C₁-C₁₈)alkyl;

(c) (C₁-C₁₈)alkyl substituted by one or more of

(1) phenyl;

15

(2) phenyl substituted by 1-5 fluoro, 1-3 halo (other than fluoro),
 1-3(C₁-C₆)alkoxy, 1-3(C₁-C₆)alkyl, nitro, cyano, hydroxy,
 trifluoromethyl, (C₁-C₆)alkylthio, amino, 1-3
 (C₁-C₆) alkylamino, di(C₁-C₆)alkylamino, -CO₂H, -COO-
 20 (C₁-C₆)alkyl, -SO₃H, -SO₂NHR¹⁵ in which R¹⁵ is hydrogen,
 (C₁-C₆)alkyl, or $\text{---}\overset{\text{O}}{\underset{\text{||}}{\text{C}}}\text{---}\overset{\text{R}^2}{\underset{|}{\text{N}}}\text{---}\text{R}^3$ in which R² and R³ are each
 independently hydrogen or (C₁-C₆) alkyl;

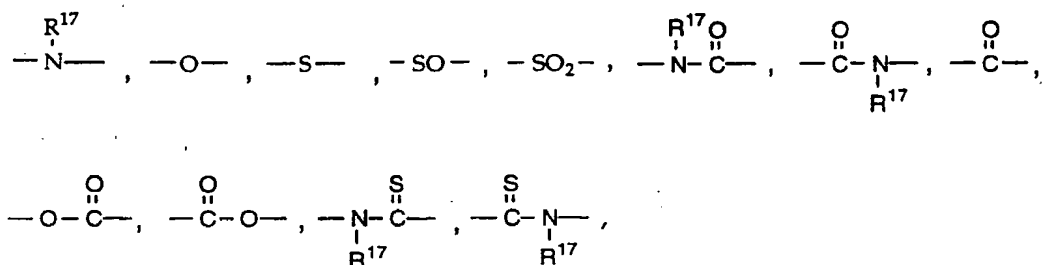
(3) heterocyclic selected from oxadiazolyl, isoxazolyl, oxazolyl,
 25 furyl and thiazolyl;

243

- (4) heterocyclic substituted by one or more of phenyl, phenyl substituted by 1-3 halo, (C₁-C₆)alkoxy, (C₁-C₆)alkyl, nitro, cyano, hydroxy, trifluoromethyl, (C₁-C₆) alkylthio, amino, (C₁-C₆) alkylamino, di(C₁-C₆) alkylamino, CO₂H, -COO-(C₁-C₆) alkyl, -SO₃H, SO₂NHR¹⁵ in which R¹⁵ is hydrogen, (C₁-C₆) alkyl, $-\overset{\text{O}}{\underset{\text{R}^2}{\text{C}}}-\text{N}-\text{R}^3$ in which R² and R³ are as defined above, (C₁-C₆) alkyl or (C₁-C₆) alkyl substituted by one or more phenyl or heterocyclic groups, said phenyl or heterocyclic group being unsubstituted or substituted by 1-3 halo, 1-3 (C₁-C₆) alkoxy, 1-3 (C₁-C₆) alkyl, nitro, cyano, hydroxy, trifluoromethyl, (C₁-C₆) alkylthio, amino, 1-3 (C₁-C₆) alkylamino, di(C₁-C₆) alkylamino, COOH, -COO-(C₁-C₆) alkyl, -SO₃H, -SO₂NHR¹⁵ in which R¹⁵ is hydrogen or (C₁-C₆) alkyl, or $-\overset{\text{O}}{\underset{\text{R}^2}{\text{C}}}-\text{N}-\text{R}^3$ in which R² and R³ are each independently hydrogen or (C₁-C₆) alkyl, the heterocyclic radical being selected from imidazolyl, oxadiazolyl, isoxazolyl, pyrrolyl, pyrazolyl, oxazolyl, furyl, thianyl or thiazolyl;
- (5) carboxy or -COO-(C₁-C₆) alkyl;
- (6) hydroxy, halo, -O-(C₁-C₆) alkyl or -S-(C₁-C₆) alkyl, with the proviso that the OH, ethers or thioethers cannot be on the carbon bearing the heteroatoms;
- (7) cyano;

244

(8) halogen, trifluoromethyl or trifluoroacetyl;

(9) $\text{CH}_2 \text{L-R}^{16}$ in which L is

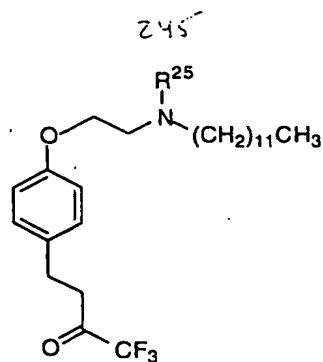
5

or $-\text{O-SiR}^{16}\text{R}^{18}\text{R}^{19}$ or a bond in which R^{16} and R^{17} are each independently (C₁-C₁₈)alkyl or (C₂-C₁₈)alkenyl or (C₁-C₁₈)alkyl or (C₂-C₁₈)alkenyl substituted by one or more phenyl or heterocyclic radicals, said phenyl or heterocyclic radicals being unsubstituted or substituted by 1-5 fluoro, 1-3 halo (other than fluoro), 1-3 (C₁-C₆)alkoxy, 1-3(C₁-C₆)alkyl, nitro, cyano, hydroxy, 1-3 trifluoromethyl, 1-3 (C₁-C₆)alkylthio, amino, 1-3(C₁-C₆)alkylamino, 1-3 di(C₁-C₆)alkylamino, CO₂H, 1-3 -COO

(C₁-C₆)alkyl, $-\overset{\text{O}}{\parallel}\text{C}-\underset{\text{R}^2}{\underset{|}{\text{N}}}-\text{R}^3$ or $-\text{SO}_2\text{NHR}^9$ in which R^9 is hydrogen or

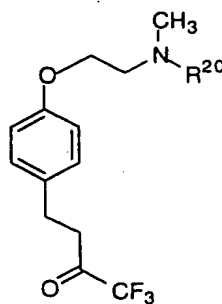
(C₁-C₆)alkyl and R^2 and R^3 are as defined above; and R^{18} and R^{19} are phenyl or phenyl substituted by 1-3 halo, (C₁-C₆) alkoxy, (C₁-C₆) alkyl, nitro, cyano, hydroxy, trifluoromethyl, (C₁-C₆) alkylthio, amino, (C₁-C₆) alkylamino, di(C₁-C₆) alkylamino, CO₂H, -COO-(C₁-C₆) alkyl, -SO₃H, SO₂NHR¹⁵ in which R^{15} is hydrogen or (C₁-C₆) alkyl, or $-\overset{\text{O}}{\parallel}\text{C}-\underset{\text{R}^2}{\underset{|}{\text{N}}}-\text{R}^3$ in which R^2 and R^3 are as defined above; or a pharmaceutically acceptable salt, solvate or prodrug thereof.

13. A compound selected from those of the following:



wherein

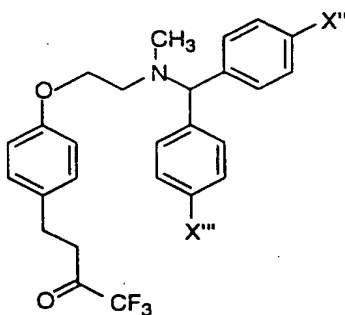
- (a) R^{25} is $-(CH_2)_3CH_3$;
- 5 (b) R^{25} is $-(CH_2)_3CO_2C_2H_5$;
- (c) R^{25} is $-(CH_2)_3CONHC_2H_5$;
- 10 (d) R^{25} is $-COCF_3$;
- (e) R^{25} is $-COC_6H_5$; and
- (f) R^{25} is $-PO(OC_2H_5)_2$; or a pharmaceutically acceptable salt thereof.
- 15
14. A compound selected from those of the following:



20 wherein

246

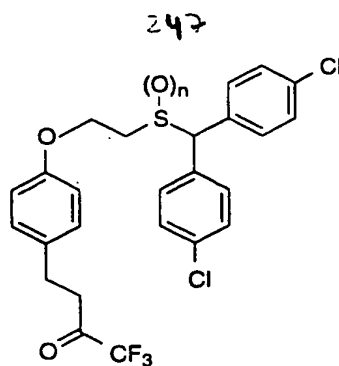
- (a) R^{20} is $-\text{CO}(\text{CH}_2)_{10}\text{CH}_3$;
- (b) R^{20} is $-\text{COCH}(\text{p-chlorophenyl})_2$; and
- 5 (c) R^{20} is $-\text{SO}_2(\text{CH}_2)_{11}\text{CH}_3$; or a pharmaceutically acceptable salt thereof.
15. A compound selected from those of the following:



10

wherein

- (a) X^{II} and X^{III} are Cl;
- 15 (b) X^{II} and X^{III} are F;
- (c) X^{II} and X^{III} are OCH_3 ; or
- (d) X^{II} is Cl and X^{III} is OCH_3 ; or a pharmaceutically acceptable salt
- 20 thereof.
16. A compound selected from those of the following:



wherein

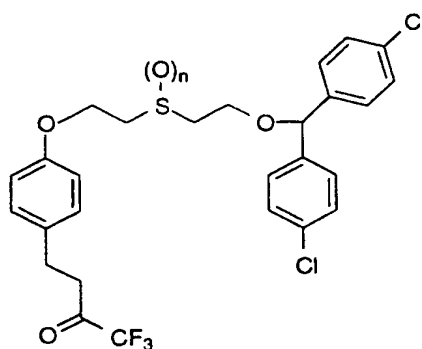
5 (a) n is 0;

(b) $n = 1$; and

(c) $n = 2$; or a pharmaceutically acceptable salt thereof.

10

17. A compound selected from those of the following:



15 wherein

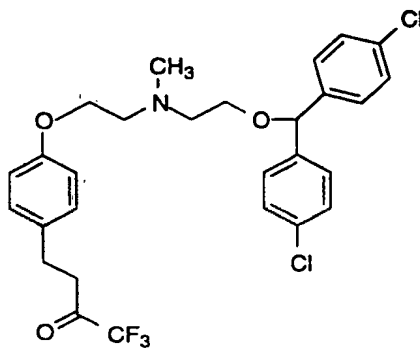
(a) $n = 0$;

(b) $n = 1$; and

248

(c) $n = 2$; or a pharmaceutically acceptable salt thereof.

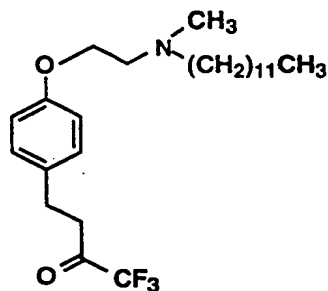
18. A compound of the formula:



5

or a pharmaceutically acceptable salt thereof.

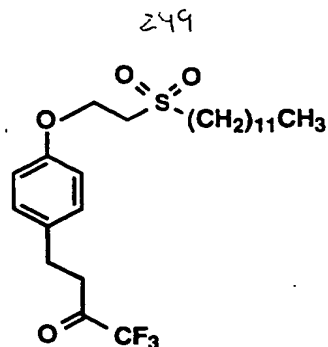
10 19. A compound of the formula



or a pharmaceutically acceptable salt thereof.

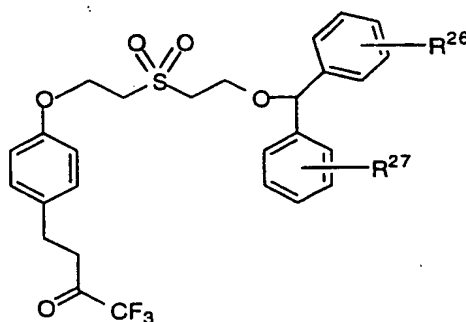
15

20. A compound of the formula



or a pharmaceutically acceptable salt thereof.

21. A compound selected from those of the following:

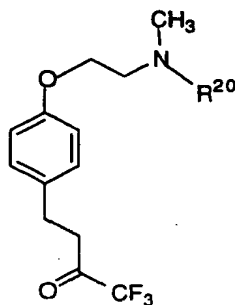


wherein

- (a) R^{26} and R^{27} are both CH_3 or $-(\text{C}_1\text{-C}_6)\text{alkyl-CF}_3$;
- (b) R^{26} and R^{27} are both Cl, F or Br;
- (c) X^a and X^b are both OCH_3 or SCH_3 ;
- (d) X^a is Cl and X^b is OCH_3 ; and
- (e) X^a and X^b are both $\text{CO}_2-(\text{C}_1\text{-C}_6)\text{alkyl}$; or a pharmaceutically acceptable salt thereof.

250

22. A compound selected from those of the following:

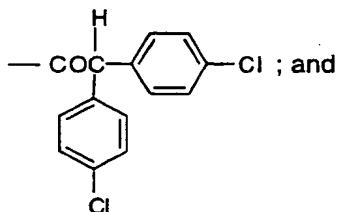


5

wherein

(a) R^{20} is $-\text{CO}(\text{CH}_2)_{10}\text{CH}_3$;

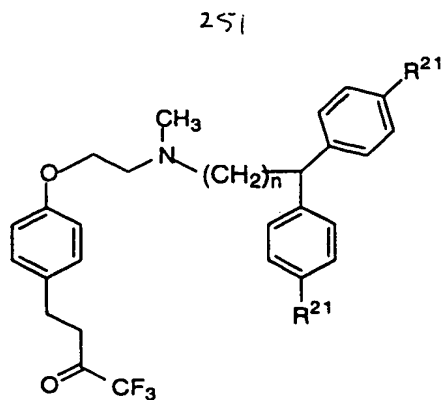
10 (b) R^{20} is



(c) R^{20} is $-\text{SO}_2(\text{CH}_2)_{11}\text{CH}_3$; or a pharmaceutically acceptable salt thereof.

15

23. A compound selected from those of the following:

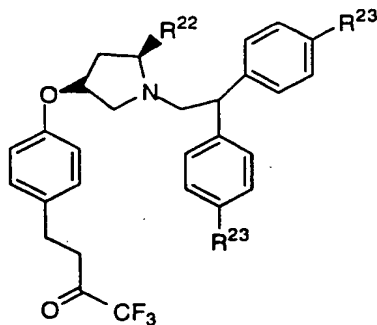


wherein

- 5 (a) n is 1 and R^{21} is OCH_3 ;
- (b) n is 1 and R^{21} is Cl ;
- (c) n is 2 and R^{21} is OCH_3 ; and
- 10 (d) n is 1-4 and R^{21} is OCH_3 or Cl ; or a pharmaceutically acceptable salt thereof.

24. A compound selected from those of the following:

15



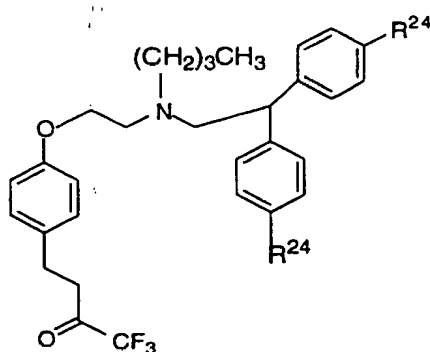
wherein

252

- (a) R^{22} is hydrogen and R^{23} is Cl;
- (b) R^{22} is $-\text{CO}_2\text{CH}_3$ and R^{23} is $-\text{OCH}_3$; or a pharmaceutically acceptable salt thereof.

5

25. A compound selected from those of the following:

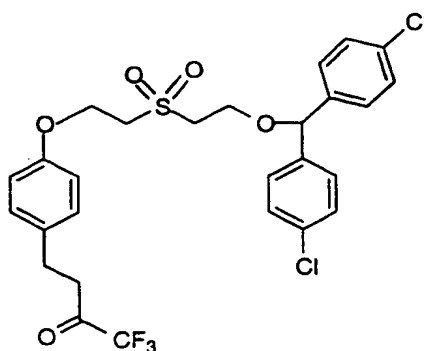


10 wherein

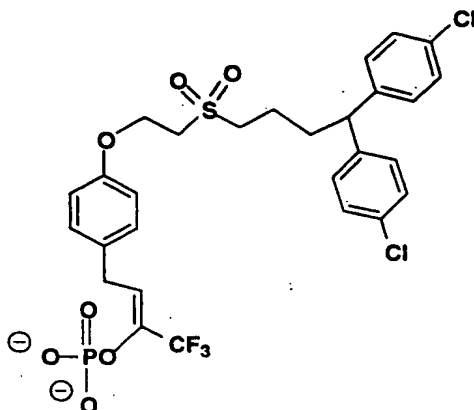
- (a) R^{24} is Cl; and
- (b) R^{24} is $-\text{OCH}_3$; or a pharmaceutically acceptable salt thereof.

15

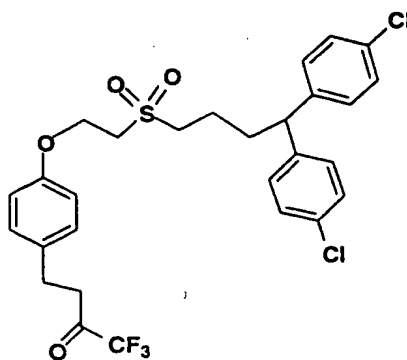
26. The compound of the formula



27. The compound of the formula

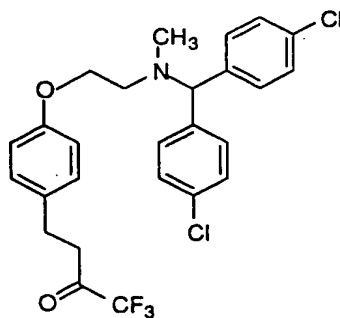


5 28. The compound of the formula



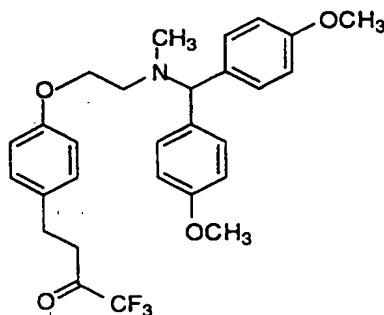
29. The compound of the formula

10

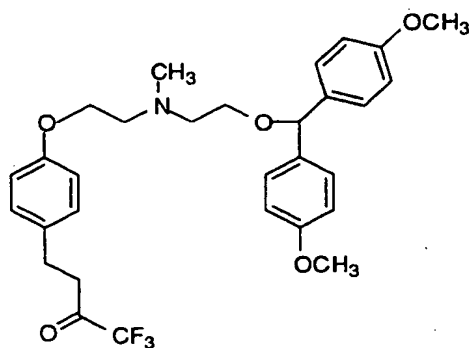


254

30. The compound of the formula

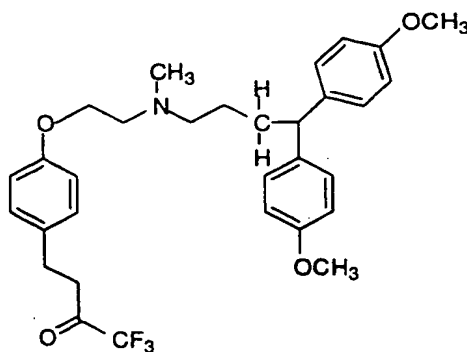


5 31. A compound of the formula



32. The compound of the formula

10



255

33. A pharmaceutical composition for the inhibition of cytosolic phospholipase A₂ comprising a therapeutically effective amount of a compound of claim 1 and a pharmaceutically acceptable carrier.

- 5 34. A method of inhibiting cytosolic phospholipase A₂ in a mammal in need thereof, comprising administering to said mammal a therapeutically effective amount of a compound of claim 1.

10

15

20

25

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
1 April 1999 (01.04.1999)

PCT

(10) International Publication Number
WO 99/15129 A3

(51) International Patent Classification⁶: **A61K 31/135**,
31/165, 31/18, 31/215, 31/40, C07C 217/54, 235/20,
237/20, 311/04, 317/24, C07D 207/12, C07F 9/02

(21) International Application Number: PCT/US98/19426

(22) International Filing Date:
17 September 1998 (17.09.1998)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/059,597 23 September 1997 (23.09.1997) US
60/063,518 27 October 1997 (27.10.1997) US

(71) Applicant: **BRISTOL-MYERS SQUIBB COMPANY**
[US/US]; 5 Research Parkway, Wallingford, CT 06492
(US).

(72) Inventors: **BANVILLE, Jacques**; 1209 Girard, St-Hu-
bert, Quebec J4T 1H3 (CA). **GAI, Yonghua**; 325 François
Leber, La Prairie, Quebec J5R 5M1 (CA). **JOHNSON,**
Graham; 57 Bridle Path Lane, Madison, CT 06443 (US).
ZUSI, Fred, Christopher; 10 Nolan Road, Hamden, CT
06514 (US). **BURKE, James, R.**; 32 Windridge Court,
Williamsville, NY 14221 (US).

(74) Agent: **MORSE, David, M.**; Bristol-Myers Squibb Com-
pany, 5 Research Parkway, Wallingford, CT 06492 (US).

(81) Designated States (*national*): AL, AM, AT, AU, AZ, BA,
BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES,
FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR,
KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW,
MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL,
TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW.

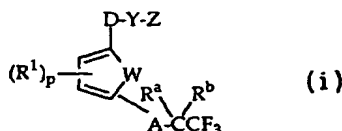
(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ,
BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE,
CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC,
NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA,
GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— with international search report

(88) Date of publication of the international search report:
26 July 2001

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: SELECTIVE cPLA₂ INHIBITORS



(57) Abstract: Selective inhibitors of the cPLA₂ enzymes are provided which are of use in controlling a wide variety of inflammatory diseases. The inhibitors of the present invention have general formula (i), where (R¹), p, D, Y, Z, R^a, R^b and A are as defined in the specification.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/19426

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NoneElectronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,238,598 A (KURIMOTO et al.) 24 August 1993, see entire document.	1-34
A	US 4,962,024 A (SHULTE) 09 October 1990, see entire document.	1-34
X	Chem. abstr., Vol. 122, 1995 (Columbus, OH, USA), the abstract No. 213907, GRIEF et al. 'Synthesis of CF ₃ -substituted quinolines from .beta.-chloro-.beta.-trifluoromethyl- vinylaldehydes. I.' J. Prakt. Chem./Chem.-Ztg. 1995, 337(1), 34-7 (German).	12
--		-----
Y		12

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

01 FEBRUARY 1999

Date of mailing of the international search report

22 FEB 1999

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized Officer

PETER G. O'SULLIVAN

Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/19426

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chem. abstr., Vol. 114, 1991, (Columbus. OH, USA), the abstract No. 97555, DINTEN et al., 'Lifetime of neutral-carrier- based liquid membranes in aqueous samples and blood and the lipophilicity of membrane components.' Anal. Chem. 1991, 63(6), 596-603 (English).	12
--		---
Y		12

Form PCT/ISA/210 (continuation of second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/19426

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (6):

A61K 31/135, 31/165, 31/18, 31/215, 31/40; C07C 217/54, 235/20, 237/20, 311/04, 317/24; C07D 207/12; C07F 9/02

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

514/424, 541, 579, 605, 617, 619, 625, 628, 648, 651, 678, 689; 548/556; 554/65; 560/39; 562/23; 564/12, 97, 165, 185, 213, 353, 354, 321, 374; 568/31

B. FIELDS SEARCHED

Minimum documentation searched

Classification System: U.S.

514/424, 541, 579, 605, 617, 619, 625, 628, 648, 651, 678, 689; 548/556; 554/65; 560/39; 562/23; 564/12, 97, 165, 185, 213, 353, 354, 321, 374; 568/31